의학박사 학위논문

Effects of multiple dosing of dexamethasone on the pharmacokinetics of oseltamivir through carboxylesterase 1 modulation in healthy volunteers

건강 자원자에서 덱사메타손 반복투여에 의한 carboxylesterase 1 조절을 통한 오셀타미비어의 약동학 변화에 관한 연구

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ABSTRACT

Introduction: Oseltamivir is widely used in the treatment and prophylaxis of influenza A and B viral infections. Dexamethasone may have beneficial effects in the treatment of acute respiratory distress syndrome, a severe complication of influenza. Carboxylesterase (CES) 1 predominantly converts oseltamivir into its active metabolite, oseltamivir carboxylate, in the liver, and dexamethasone modulates the expression of CES1. However, the effects of dexamethasone on the pharmacokinetics (PK) of oseltamivir remain unclear. The aim of this study was to investigate the effects of co-administration of oseltamivir and dexamethasone on the PK of oseltamivir in healthy volunteers.

Methods: An open-label, two-period, one-sequence, multiple-dose study was conducted in 19 healthy male volunteers. Oseltamivir (75 mg) was orally administered on Day 1 and Day 8, and dexamethasone (1.5 mg) was administered once daily from Day 3 to Day 8. Serial blood and urine samples were collected for PK analysis of oseltamivir and oseltamivir carboxylate on Day 1 and Day 8. In addition, a genotype test was performed on Day 1 to identify the CES1 genotype. Oseltamivir and oseltamivir carboxylate concentrations in plasma and urine were determined using liquid chromatography–tandem mass spectrometry.

Results: After dexamethasone treatment for 6 days, the area under the plasma concentration–time curve (AUC) of oseltamivir and oseltamivir carboxylate decreased by 4% ($P = 0.21$) and 12% ($P < 0.0001$), respectively. The geometric mean ratio (90% confidence interval) of the metabolic ratio (oseltamivir carboxylate $AUC_{0–48h}$/oseltamivir $AUC_{0–48h}$) was 0.92 (0.87–0.97; $P = 0.02$).

The amount of unchanged oseltamivir excreted in urine increased by 14% after dexamethasone treatment ($P = 0.08$).

Conclusions: These findings suggest that the co-administration of low-dose dexamethasone and oseltamivir may decrease the systemic exposure to oseltamivir and oseltamivir carboxylate by the inhibition of CES1. However, the co-administration does not appear to have a clinically relevant effect on the PK of oseltamivir. Therefore, low-dose dexamethasone can be co-administered with oseltamivir without dose adjustment.

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Keywords: Oseltamivir, Dexamethasone, Carboxylesterase, Drug-drug interaction

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LIST OF ABBREVIATIONS

Ae	Amount of urine excreted
$Ae_{0\text{-}24h}$	Ae from 0 to 24 hours
ARDS	Acute Respiratory Distress Syndrome
AUC	Area under the concentration-time curve
$AUC_{0\text{-}12h}$	AUC from 0 to 12 hours
$AUC_{0\text{-}48h}$	AUC from 0 to 48 hours
AUC_{inf}	AUC from 0 to infinite time
CES	Carboxylesterase
CI	Confidence intervals
CL	Clearance
CL_r	Renal clearance
CL/F	Apparent clearance
C_{max}	Maximum concentration
CTC	Clinical Trial Center
CYP	Cytochrome P450
ECG	Electrocardiography
GMR	Geometric Mean Ratio
GR	Glucocorticoid receptor
IRB	Institutional Review Board
LLOQ	Lower Limit of Quantification
MR	Metabolic ratio

mRNA	messenger RNA
MS/MS	Tandem mass spectrometry
NR	Nuclear receptor
PD	Pharmacodynamics
PK	Pharmacokinetics
PXR	Pregnane X receptor
SD	Standard deviation
SNP	Single Nucleotide Polymorphism
$t_{1/2}$	Terminal elimination half-life
T_{max}	Time to C_{max}
λ_z	Apparent terminal elimination rate constant

INTRODUCTION

Oseltamivir is an antiviral medicine which is widely used in the treatment and prophylaxis of influenza A and B viral infections (1-3). It is readily absorbed from the gastrointestinal tract after oral administration and is predominantly converted by carboxylesterase (CES) 1 into its active metabolite oseltamivir carboxylate, which is an inhibitor of neuraminidase in the influenza virus (2, 4). At least 75% of the oral dose of oseltamivir enters systemic circulation as oseltamivir carboxylate (2, 4). The renal elimination of oseltamivir carboxylate accounts for more than 99% of the administered dose (3-5). In general, the recommended dose for curative treatment in adults with normal renal function is 75 mg twice a day for 5 days (6).

CES is an important phase I enzyme that catalyzes the hydrolysis of many endogenous and exogenous substrates such as ester, amide, carbamates, and thioesters (7). In humans, the CES enzyme is present as two main isozymes: CES1 and CES2. The level of expression of these isozymes differs among organs. CES1 is highly expressed in the liver, whereas the expression of CES2 is high in the intestine (8, 9). CES1 plays an important role in the hydrolysis of various drugs, such as angiotensin-converting enzyme inhibitors, statins, central nervous system stimulants, immunosuppressants, and antiviral agents (10,11). CES1 activity is a major determinant of the pharmacokinetics (PK) and pharmacodynamics (PD) of these drugs (9). The modulation of CES activity may alter drug metabolism and PK, which may lead to drug toxicity or improve efficacy. In particular, the genetic polymorphism of the human CES1 enzyme

and CES inhibitors or inducers can affect the activity of CES, significantly affecting the therapeutic effects of its substrate drugs (7).

Previous studies, including *in vitro* and *in vivo* studies, have shown that CES1 genetic variants, such as c.428G>A (p.Gly143Glu, rs121912777) and c.780delT (p.Asp260fs, rs71647872), were anticipated to reduce the activity of CES1. This can alter the PK characteristics of CES substrates in humans, including oseltamivir, methylphenidate, enalapril, and clopidogrel (12-16). However, these CES1 genetic variants have not been identified in Asians and are rarely found in Caucasian, black, and Hispanic populations (12, 17). Therefore, we identified 41 single nucleotide polymorphisms (SNPs), including 14 non-synonymous variants of CES1 in 200 Koreans to identify a novel CES genetic variant that could alter the CES1 activity in Korean (17). Based on an in silico analysis using the PolyPhen-2 software (http://genetics.bwh.harvard.edu/pph2/), three SNPs (c.662A>G, rs200707504; c56G>T, rs3826190; and c.808G>T, rs115629050) were expected to be associated with decreased CES1 activity. Their minor allele frequencies in Koreans were 2%, 1.5%, and 0.8%, respectively, compared with 4.57% in the global population (17-19). We evaluated the effects of the c.662A>G SNP on the PK of oseltamivir in humans. A single oral dose of oseltamivir (75 mg) was administered to 20 healthy subjects, eight heterozygous c.662A>G carriers (c.662AG) and twelve non-carriers (c.662AA). The area under the plasma concentration–time curve $(AUC)_{0–48h}$ of oseltamivir, increased by 10% in the c.662AG carriers, whereas the $AUC_{0–48h}$ of oseltamivir carboxylate of them decreased by 5%. These results suggest that CES1 activity may be reduced in

these heterozygous allele carriers.

Co-administration with a CES inhibitor or inducer could affect the therapeutic activity of drugs that are substrates of CES (7). For instance, ethanol, an inhibitor of CES1, prevents the hydrolysis of methylphenidate into ritalinic acid, leading to elevated methylphenidate C_{max} and AUC values (7,20). Increased absorption rate and/or C_{max} of methylphenidate correlates with the potential for methylphenidate abuse (20). Moreover, in a previous study, clopidogrel was found to inhibit the CES1-mediated hydrolysis of oseltamivir into its active metabolite by 90%, rendering oseltamivir therapeutically inactive (21).

Multiple therapeutic agents are combined with oseltamivir to treat the symptoms of influenza or to achieve synergistic effects because patients with H5N1 influenza usually develop severe pneumonia. Dexamethasone, a type of steroid, is used to treat various inflammatory and autoimmune diseases. In particular, steroids may have beneficial effects in acute respiratory distress syndrome (ARDS), a severe complication of influenza (22), and are likely to be used with oseltamivir. Thus, there is potential for clinically relevant drug interactions between oseltamivir and dexamethasone. Dexamethasone is a moderate inducer of cytochrome P450 3A4 (CYP3A4); however, the effects of dexamethasone on CES remain controversial. A study conducted by Takahashi et al in 2009 demonstrated that dexamethasone weakly (>50% of control) inhibits the formation of imidaprilat from imadipril by CES1 in the human liver (23). A study by Zhu et al demonstrated that the exposure of cultured human hepatocytes to dexamethasone causes a marginal increase (~20%) in human

CES1 and CES2 levels (24). The inductive effects were concentration-dependent and were observed only at higher concentrations of dexamethasone (≥10 μM).

Many people may be exposed to oseltamivir during an influenza pandemic, and drug interactions between oseltamivir and dexamethasone can occur through the inhibition or induction of CES. Therefore, the effect of genetic polymorphism and the co-administration of inhibitors and/or inducers of CES need to be evaluated. Drug interactions between oseltamivir and dexamethasone can occur through the inhibition or induction of CES, which could change the PK and PD of oseltamivir. Conflicting results have been obtained in studies examining the influence of dexamethasone on CES activity. However, data for drug interaction between oseltamivir and dexamethasone in humans are insufficient. Therefore, further studies are required to determine the potential drug interactions between oseltamivir and dexamethasone in humans as well as the underlying mechanisms. This study was conducted to evaluate the effects of the administration of multiple doses of dexamethasone for 6 days on the PK of oseltamivir and oseltamivir carboxylate in healthy volunteers.

MATERIALS AND METHODS

This study was conducted at the Clinical Trials Center (CTC), CHA Bundang Medical Center, Seongnam, South Korea in compliance with the ethical principles of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice Guideline, and local laws and regulations. The protocol was approved by the Institutional Review Board (IRB) of CHA Bundang Medical Center and registered at National Research Institute of Health (CRIS: KCT0001533). All the subjects provided written informed consent after a detailed explanation of the study prior to any study procedure.

Subjects

Males 20–45 years of age with a body mass index (BMI) of 19–27 kg/m^2, and who were in good general health based on a detailed medical history, physical examination, vital signs, electrocardiography (ECG), and clinical laboratory evaluations (including hematology, liver function tests, renal function tests, blood glucose, urinalysis (including urine drug screening), and seroimmunology (hepatitis B surface antigen, anti-hepatitis C virus antibody, and anti-human immunodeficiency virus antibody) were included in this study. Subjects were excluded if they had a history of significant gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, or hormonal disorders; a history of drug or food allergies; taken any prescription

medication within 2 weeks prior to the first administration of the study drug; a diet that would affect the absorption, distribution, metabolism, and elimination of the drugs; a positive drug or alcohol screening; smoked 10 or more cigarettes per day within 3 months; or participated in a clinical trial during the last 3 months prior to the start of the study.

Study design

An open-label, two-period, single-sequence study was performed (**Figure 1**). Twenty healthy Korean male subjects were enrolled. All subjects were admitted to the CTC at CHA Bundang Medical Center on the day before oseltamivir administration in period 1. On the following day (Day 1) after overnight fasting, a single dose of 75 mg oseltamivir (Tamiflu® Capsule; Roche Registration Ltd., Welwin Garden City, United Kingdom) was orally administered with 240 mL of water, and serial blood and urine samples for PK evaluation were taken over 48 h. In addition, a genotype test was performed on Day 1 to identify the CES 1 genotype. Daily doses of dexamethasone (0.5 mg X 3 tablets, Dexamethasone® Tab., YuhanMedica, Seoul, Korea) were administered orally for six days every morning from Day 3 to Day 8. On Day 8, oseltamivir and dexamethasone were co-administered orally at the same time in the morning, and subjects underwent the same procedure as they did in period 1 (**Figure 1**).

For PK analysis of oseltamivir and oseltamivir carboxylate, blood samples were collected at 0 (ie, pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 48 h post dose; urine samples were collected up to 24 h post dose. Tolerability was evaluated throughout the entire study period by examining the

incidence and type of adverse events (AEs), as well as changes in clinical laboratory test values, physical examinations, vital signs, and 12-lead ECGs.

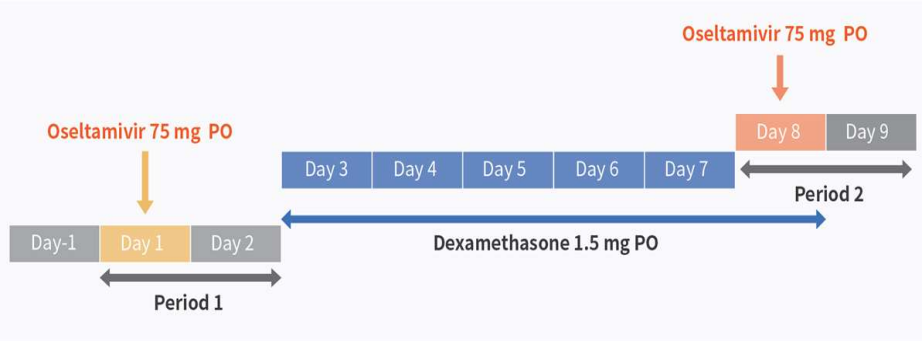

Figure 1. Study flowchart

Notes: Oseltamivir 75 mg, 1 capsule (Tamiflu®, Roche) and dexamethasone 0.5 mg, 3 tablets (Dexamethasone Tab., YuhanMedica) were used.

Determination of oseltamivir and oseltamivir carboxylate concentration

Oseltamivir and oseltamivir carboxylate concentrations in plasma and urine were determined using a highly specific and sensitive method of liquid chromatography–tandem mass spectrometry (Agilent 6490 Triple Quadrupole, Agilent Technologies, Santa Clara, CA, USA). To prepare the samples for analysis, an aliquot of the plasma or urine specimen was mixed with acetonitrile in the presence or absence of oseltamivir carboxylate-d3, which was used as an internal standard. The mixture was vortexed for 30 seconds and then centrifuged for 10 min at 14,000 rpm. An aliquot of the supernatant was transferred to an autosampler vial, and 2 μL was injected onto a Kinetex HILIC column (50 mm × 2.1 mm, 5 μm; Phenomenex, Torrance, CA, USA) with a 3 min run at a flow rate of 0.3 mL/min using gradient elution. Mobile phase A consisted of 10 mM ammonium acetate in water and mobile phase B consisted of 100% acetonitrile. Oseltamivir and oseltamivir carboxylate were quantitatively detected in the positive ionization of triple-quadrupole mass spectrometry equipped with electrospray ionization. The method was validated with a range of 0.5–100 ng/mL and 20–20,000 ng/mL for oseltamivir in plasma and urine, respectively, and 2–500 ng/mL and 500–100,000 ng/mL for oseltamivir carboxylate in plasma and urine, respectively.

Pharmacokinetics data analysis

Plasma concentrations of oseltamivir and oseltamivir carboxylate were

analyzed by noncompartmental analysis using Phoenix® WinNonlin® software version 1.3 (Certara, St. Louis, MO, USA). The area under the concentration-time curve (AUC) for oseltamivir and oseltamivir carboxylate from time 0 to 48 h post dose ($AUC_{0\text{-}48h}$) was calculated using the linear up, log down trapezoidal method. In addition, AUC from time zero to infinite time (AUC_{inf}) was calculated as the sum of $AUC_{0\text{-}48h}$ and the last quantifiable concentration divided by the slope of the final decline portion of the individual log-linear concentration-time curve. The metabolic ratio was calculated as oseltamivir carboxylate $AUC_{0\text{-}48h}$/ oseltamivir $AUC_{0\text{-}48h}$. The observed concentrations and times were used to estimate the maximum concentration (C_{max}) and time to reach the C_{max} (T_{max}) for oseltamivir and oseltamivir carboxylate. The apparent terminal elimination rate constant (λ_z) was estimated from a regression of log transformed plasma concentrations of oseltamivir and oseltamivir carboxylate versus time over the terminal log-linear disposition portion of the concentration-time profiles. The elimination half-life ($t_{1/2}$) was calculated as the natural logarithm of 2 divided by λ_z. Total apparent clearance (CL/F) of oseltamivir was calculated as the administered dose (75 mg) over the $AUC_{0\text{-}48h}$ (oseltamivir) and the apparent volume of distribution was calculated as the CL/F divided by λ_z. Total urinary excreted amount of oseltamivir and oseltamivir carboxylate during 24 hours ($Ae_{0\text{-}24h}$) was calculated by multiplying the volume of excreted urine and urinary concentration of oseltamivir and oseltamivir carboxylate, respectively.

Genotyping of CES1 c.662A>G SNP

Genomic DNA samples were extracted using a QIAamp DNA Mini Kit (QIAgen, Hilden Germany). The PCR reaction included a target gene specific primer pairs (CES1-1F: ctgtggtcctgaaggtcctg; CES1-1R: caaccaagctggaagaggag) and Dr. MAX DNA Polymerase (Doctor Protein INC, Seoul, Korea). The PCR amplification conditions consisted of 94 °C for 5 min; 35 cycles of 94 °C for 30 seconds, variable temperature for 30 sec, and 72 °C for 40 sec; and finally 72 °C for 7 min. The PCR products were purified using a Millipore plate MSNU030 (Millipore SAS, Molsheim, France). The purified PCR products were then Sanger-sequenced from on an ABI PRISM 3730xl automated sequencer (Applied Biosystems, Foster City, CA, USA) with the BigDye Terminator Sequencing Kit v3.1. The nucleotide sequences of both strands of the PCR amplification products were determined in the Macrogen Sequencing Facility (Macrogen Inc., Seoul, Korea). The CES1 SNP genotyping was focused on c.662A>G and not on other CES1 SNPs.

Statistical analysis

The target sample size was chosen to address the primary pharmacokinetic study objective, which was to demonstrate that dexamethasone does not have a significant effect on oseltamivir carboxylate pharmacokinetics as measured by C_{max} and $AUC_{0\text{-}48h}$. The absence of a significant effect was considered to have been demonstrated if the 90% confidence interval (CI) for the ratio of test to reference (i.e. test: oseltamivir with dexamethasone; reference: oseltamivir alone) lay within the range (0.80 to 1.25) for the C_{max} and $AUC_{0\text{-}48h}$ (as per FDA

guidance for bioequivalence). Assuming the within-subject coefficient of variation (CV) was not larger than 18.8% (based on in house data previously performed by Oh et al.), it was estimated that enrolling 20 subjects, to ensure a sample size of 17 subjects with all studies completed, would provide at least 90% power to demonstrate no effect of dexamethasone administration on the oseltamivir carboxylate C_{max} or $AUC_{0\text{-}48h}$.

All of the demographic characteristics and PK parameters are presented as arithmetic means and standard deviation (SD). A general linear model was developed to estimate the geometric mean ratios (GMRs) of the PK parameters and their 90% confidence intervals (CIs) for oseltamivir and its metabolite (oseltamivir carboxylate). Differences were considered statistically significant when *P*-values were less than 0.05. Statistical analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study population

In total, 31 volunteers were screened; 22 healthy subjects were enrolled, but 19 (86.4%) of whom completed the study. Two subjects (Subject ID: AN02, AN10) withdrew consent prior to administration of oseltamivir on Day 1 and one subject (Subject ID: AN14) withdrew consent prior to administration of dexamethasone on Day 3, respectively. The mean ± SD of age, body weight, and body mass index was 27.7 ± 3.8 years, 70.7 ± 6.7 kg, and 23.0 ± 1.7 kg/m^2, respectively. All subjects had the c.662AA genotype. (**Table 1**)

Table 1. Individual demographic data

ID	Age (Years)	Weight (kg)	Height (m)	BMI (kg/m^2)	c.662A>G SNP
AN01	22	55.8	1.69	19.5	c.662AA
AN03	22	68.6	1.78	21.7	c.662AA
AN04	21	61.9	1.68	21.9	c.662AA
AN05	23	63.4	1.73	21.2	c.662AA
AN06	23	59.7	1.63	22.5	c.662AA
AN07	22	72.1	1.78	22.8	c.662AA
AN08	37	62.7	1.66	22.8	c.662AA
AN09	26	79.2	1.83	23.6	c.662AA
AN11	23	69.0	1.68	24.4	c.662AA
AN12	43	65.5	1.71	22.4	c.662AA
AN13	24	70.3	1.76	22.7	c.662AA
AN15	24	80.8	1.83	24.1	c.662AA
AN16	24	66.9	1.77	21.4	c.662AA
AN17	27	62.8	1.71	21.5	c.662AA
AN18	27	57.5	1.67	20.6	c.662AA
AN19	27	71.4	1.71	24.4	c.662AA
AN20	33	67.4	1.78	21.2	c.662AA
AN21	23	67.0	1.72	22.6	c.662AA
AN22	37	74.9	1.76	24.1	c.662AA

Plasma oseltamivir and oseltamivir carboxylate concentration profiles

After a single oral administration of oseltamivir with or without dexamethasone, oseltamivir was rapidly absorbed (median T_{max}: 0.5 hour for oseltamivir alone and 1 hour for oseltamivir with dexamethasone coadministration, **Table 2**) and converted to oseltamivir carboxylate in all subjects (**Figure 2, Figure 3**). In 9 (47.7%) on 19 subjects, a small second peak concentration of oseltamivir was observed, at a median (range) 3 hour (1.5 – 5 hour) with a median (range) of 66.3% (38.4 – 141.6%) compared to the first peak (**Supplementary Figure 1**).

Effects of Dexamethasone on Oseltamivir PK

The concentration-time profiles for oseltamivir before dexamethasone treatments were comparable to those after 6 days of dexamethasone administrations (**Table 2; Figure 2, Figure 3** and **Figure 4**). Furthermore, the systemic exposure of oseltamivir, based on $AUC_{0\text{-}48h}$ and AUC_{inf}, in subjects co-administered with dexamethasone and subjects who were not administered dexamethasone fell entirely within the conventional bioequivalence range of 80-125% (**Table 2**). It was slightly lower 4% and 5%, respectively than that of subjects that were not administered dexamethasone, although this difference was not statistically significant (**Table 2; Figure 4**).

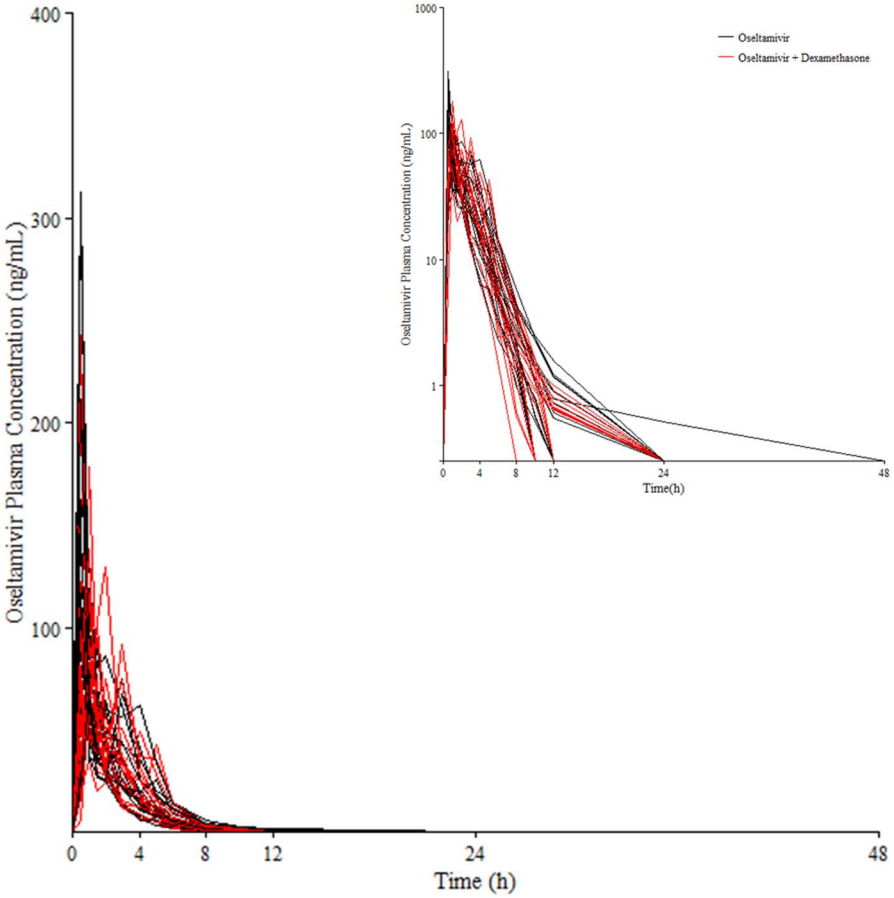

Figure 2. Individual plasma concentration-time profiles of oseltamivir after a single oral administration of oseltamivir at 75 mg and a single oral administration of oseltamivir at 75 mg after 6 days of dexamethasone 1.5 mg treatments.

Notes: Inserted figure is a semi-log scale individual plasma concentration time profiles. The LLOQ for oseltamivir was 0.5 ng/mL.

Table 2. Pharmacokinetic parameters of oseltamivir after a single dose of oseltamivir (75 mg) orally administered and a single dose of oseltamivir (75 mg) co-administered with dexamethasone after 6 days of dexamethasone (1.5 mg) treatment.

PK parameters		Oseltamivir		GMR* (90% CI)	*P*-value‡
		Oseltamivir alone (n=19)	Oseltamivir + Dexamethasone (n=19)		
T_{max} (h)	median	0.5	1.0		
	range	[0.5-3.0]	[0.5-4.0]		
C_{max} (ng/mL)	mean	131.0	117.1	0.92	0.47
	SD	72.63	53.69	(0.75, 1.12)	
$AUC_{0\text{-}12h}$ (h*ng/mL)	mean	229.54	218.95	0.96	0.23
	SD	58.42	50.04	(0.90, 1.02)	
$AUC_{0\text{-}48h}$ (h*ng/mL)	mean	230.15	219.02	0.96	0.21
	SD	58.62	49.91	(0.90, 1.02)	
AUC_{inf} (h*ng/mL)	mean	232.97	221.2	0.95	0.19
	SD	58.92	50.13	(0.90, 1.01)	
$Ae_{0\text{-}24h}$ (mg)	mean	2.44	2.68	1.14	0.08
	SD	0.86	0.62	(1.01, 1.30)	
CLr (L/h)	mean	11.06	12.38	1.20	0.07
	SD	4.41	2.84	(1.02, 1.41)	

*Geometric mean ratio (90% CI) of (oseltamivir +dexamethasone) / (oseltamivir alone);
‡*P*-value was measured using a mixed effect model in SAS 9.3.

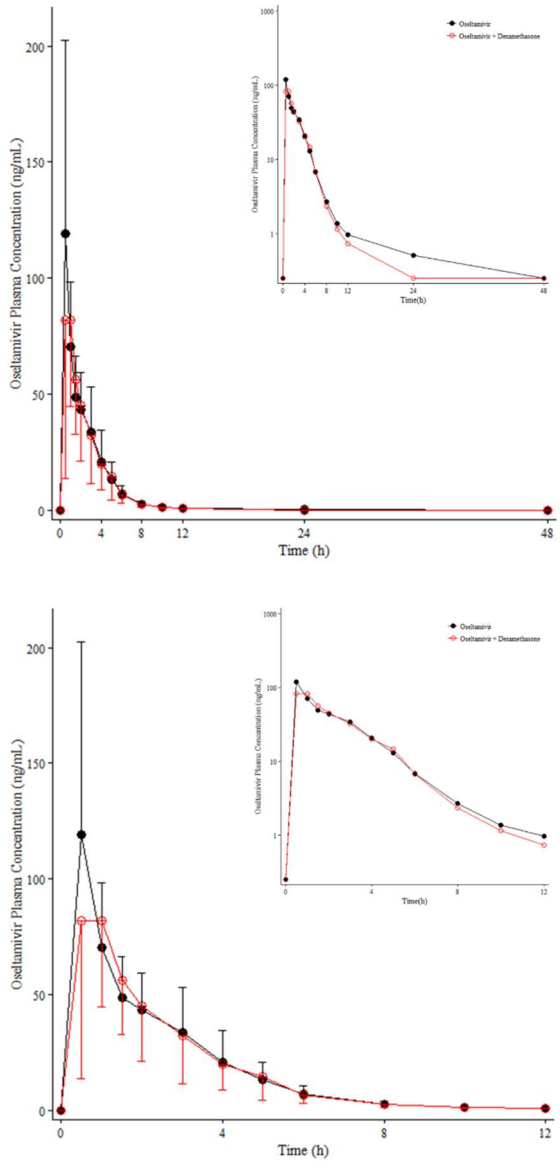

Figure 3. Mean plasma concentration-time profiles of oseltamivir until 48 hours (upper) and 12 hours (lower) after a single oral administration of oseltamivir at 75 mg and a single oral administration of oseltamivir at 75 mg after 6 days of dexamethasone 1.5 mg treatments.

Notes: The error bars represent the SD. Inserted figure is a semi-log scale mean plasma concentration time profiles. The LLOQ for oseltamivir was 0.5 ng/mL.

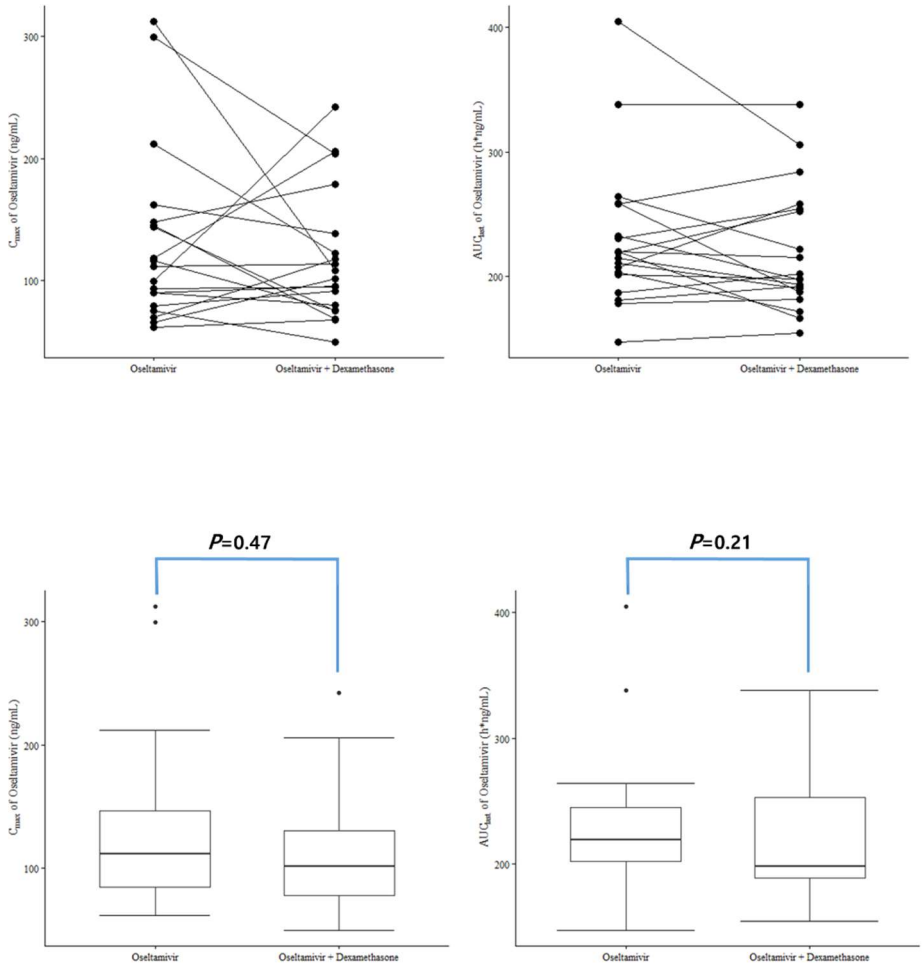

Figure 4. Comparison of C_{max} and $AUC_{0\text{-}48h}$ of oseltamivir with/without dexamethasone (upper: subject profile, lower: box plot, left: C_{max}, right: $AUC_{0\text{-}48h}$) The solid lines across the box, the top edge, and the bottom edge represent the median, the 75th percentile, and the 25th percentile, respectively. The horizontal lines connected with the whiskers extending from the box denote the 90th and 10th percentiles, respectively. The dots outside of the whiskers represent outliers.

Effects of Dexamethasone on Oseltamivir carboxylate PK

In contrast to oseltamivir, $AUC_{0\text{-}48h}$ and AUC_{inf} of oseltamivir carboxylate were approximately 12% and 11% lower, respectively, in subjects receiving multiple doses of dexamethasone than those of subjects administered oseltamivir alone, which were statistically significant outcomes (**Table 3; Figure 5, Figure 6** and **Figure 7**). The C_{max} of oseltamivir carboxylate after treatments with dexamethasone was comparable to the C_{max} observed in subjects administered oseltamivir alone (**Table 3; Figure 5** and **Figure 7**).

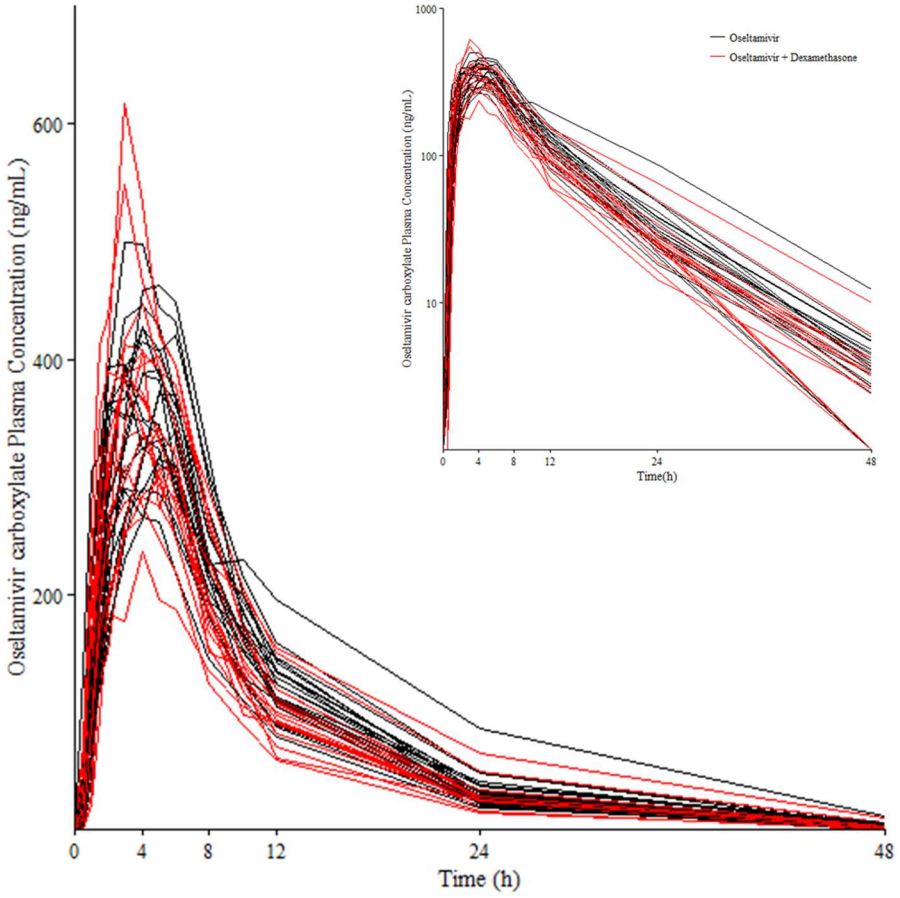

Figure 5. Individual plasma concentration-time profiles of oseltamivir carboxylate after a single oral administration of oseltamivir at 75 mg and a single oral administration of oseltamivir at 75 mg after 6 days of dexamethasone 1.5 mg treatments.

Notes: Inserted figure is a semi-log scale individual plasma concentration time profiles. The LLOQ for oseltamivir was 2.0 ng/mL.

Table 3. Pharmacokinetic parameters of oseltamivir carboxylate after a single dose of oseltamivir (75 mg) orally administered and a single dose of oseltamivir (75 mg) co-administered with dexamethasone after 6 days of dexamethasone (1.5 mg) treatment.

PK parameters		Oseltamivir carboxylate		GMR* (90% CI)	*P*-value‡
		Oseltamivir alone (n=19)	Oseltamivir + Dexamethasone (n=19)		
T_{max} (h)	median	4.0	4.0		
	range	[2.0-6.0]	[2.0-5.0]		
C_{max} (ng/mL)	mean	380.34	381.15	0.99	0.71
	SD	57.73	89.48	(0.94, 1.04)	
AUC_{0-12h} (h*ng/mL)	mean	2858.88	2658.79	0.92	0.0003
	SD	445.45	522.52	(0.89, 0.95)	
AUC_{0-48h} (h*ng/mL)	mean	4022.46	3554.85	0.88	<0.0001
	SD	709.32	712.0	(0.85, 0.91)	
AUC_{inf} (h*ng/mL)	mean	4083.08	3639.18	0.89	<0.0001
	SD	709.68	703.65	(0.87, 0.91)	
Ae_{0-24h} (mg)	mean	42.85	47.18	1.11	0.14
	SD	9.47	9.75	(0.99, 1.24)	
CLr (L/h)	mean	11.94	14.68	1.24	0.005
	SD	3.73	3.91	(1.10, 1.39)	

* Geometric mean ratio (90% CI) of (oseltamivir +dexamethasone) / (oseltamivir alone);
‡*P*-value was measured using a mixed effect model in SAS 9.3.

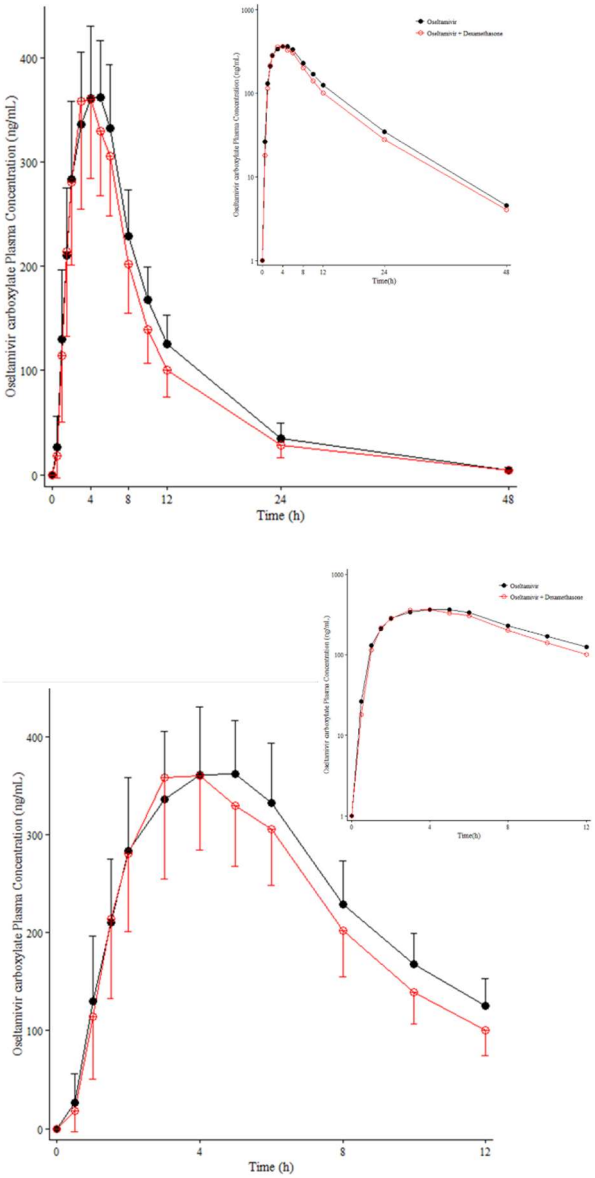

Figure 6. Mean plasma concentration-time profiles of oseltamivir carboxylate until 48 hours (upper) and 12 hours (lower) after a single oral administration of oseltamivir at 75 mg and a single oral administration of oseltamivir at 75 mg after 6 days of dexamethasone 1.5 mg treatments.

Notes: The error bars represent the SD. Inserted figure is a semi-log scale mean plasma concentration time profiles. The LLOQ for oseltamivir was 2.0 ng/mL.

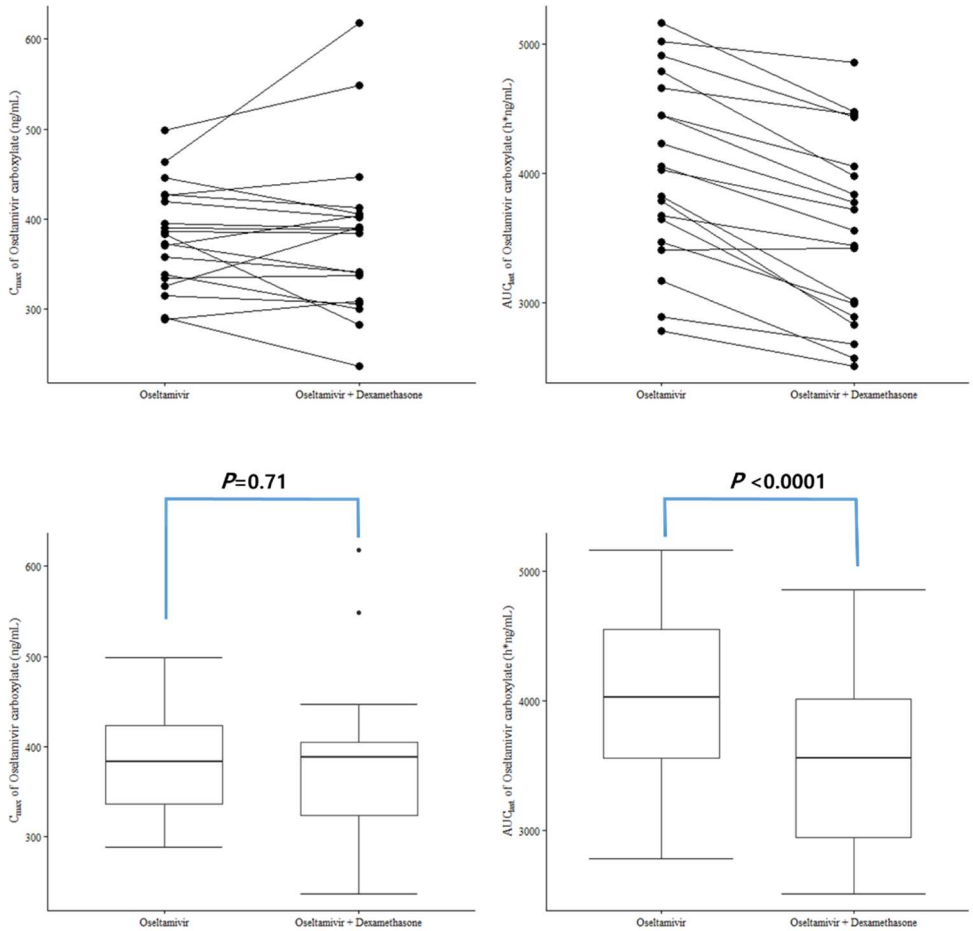

Figure 7. Comparison of C_{max} and $AUC_{0\text{-}48}$ of oseltamivir carboxylate with/without dexamethasone (upper: subject profile, lower: box plot, left: C_{max}, right: $AUC_{0\text{-}48}$) The solid lines across the box, the top edge, and the bottom edge represent the median, the 75th percentile, and the 25th percentile, respectively. The horizontal lines connected with the whiskers extending from the box denote the 90th and 10th percentiles, respectively. The dots outside of the whiskers represent outliers.

The metabolic ratio of oseltamivir was approximately 8% lower when co-administered with dexamethasone than when administered alone, which was statistically significant (**Table 4; Figure 8**). The amount of oseltamivir and oseltamivir carboxylate excreted in the urine was greater after treatment with dexamethasone, and the GMR for the $Ae_{0\text{-}24h}$ of oseltamivir and oseltamivir carboxylate was 1.14 and 1.11, respectively (**Table 1** and **Table 2**).

Table 4. Metabolic ratio of oseltamivir carboxylate after a single oral administration of oseltamivir (75 mg) and a single oral administration of oseltamivir (75 mg) after 6 days of dexamethasone (1.5 mg) treatment.

Parameters		Oseltamivir carboxylate /Oseltamivir		GMR* (90% CI)	*P*-value‡
		Oseltamivir alone (n=19)	Oseltamivir + Dexamethasone (n=19)		
Metabolic ratio	mean	18.06	16.75	0.92	0.02
	SD	3.82	4.04	(0.87, 0.97)	

Notes: The metabolic ratio was calculated as $AUC_{0\text{-}48h}$ (oseltamivir carboxylate) / $AUC_{0\text{-}48h}$ (oseltamivir). *Geometric mean ratio (90% CI) of (oseltamivir +dexamethasone) / (oseltamivir alone); ‡*P*-value was measured using a mixed effect model in SAS 9.3.

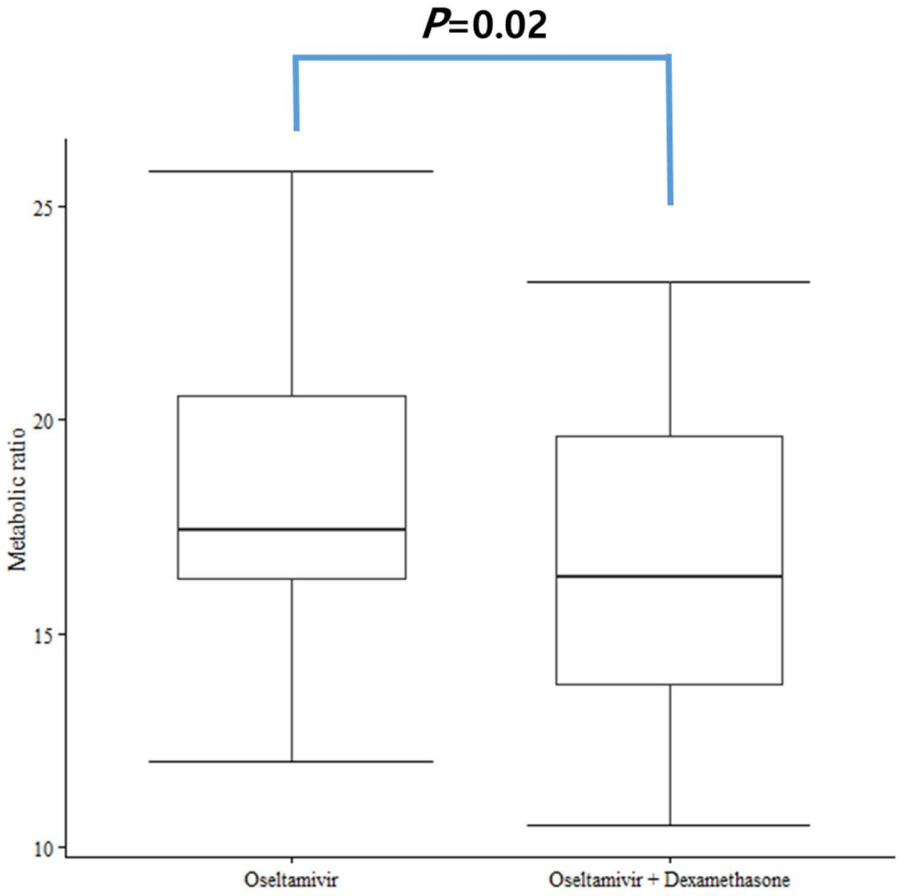

Figure 8. Comparison of metabolic ratio of oseltamivir with/without dexamethasone. The metabolic ratio was calculated as the $AUC_{0\text{-}48h}$, oseltamivir carboxylate / $AUC_{0\text{-}48h}$, oseltamivir. The solid lines across the box, the top edge, and the bottom edge represent the median, the 75th percentile, and the 25th percentile, respectively. The horizontal lines connected with the whiskers extending from the box denote the 90th and 10th percentiles, respectively. The dots outside of the whiskers represent outliers.

Tolerability

No serious AEs occurred in this study, and unexpected AEs that could have influenced the outcome of the study were not reported. Vital signs of the study subjects, including blood pressure, pulse rate, body temperature, and the physical examination results showed no clinically significant changes.

DISCUSSION

Drug–drug interactions should be evaluated as part of the safety and efficacy assessment of a drug. Oseltamivir and dexamethasone could be co-administered in case of an influenza pandemic depending on the disease status or comorbidity. Previous studies have demonstrated that dexamethasone modulates the expression of CES1 (23,24) and that oseltamivir is predominantly converted into its active metabolite by CES1 in the liver (2). Therefore, significant drug–drug interactions could occur when oseltamivir and dexamethasone are co-administered. This study was conducted to investigate the effects of co-administering dexamethasone and oseltamivir on the PK of oseltamivir in healthy volunteers. The results showed that the systemic exposure to oseltamivir carboxylate is marginally but significantly reduced after multiple administrations of dexamethasone, whereas the systemic exposure to oseltamivir is relatively unchanged regardless of the dexamethasone treatment.

In this study, we evaluated the effects of dexamethasone on oseltamivir by administering a low dose of dexamethasone (1.5 mg) for 6 days. This study was not conducted in patients with influenza or ARDS, and we used low doses of dexamethasone considering the safety of the healthy volunteers. The expression of CES is strongly controlled by nuclear receptor (NR) proteins pregnane X receptor (PXR); PXR is also known to regulate CYP3A4 (25). In an *in vitro* study by Pascussi et al., which investigated the effects of dexamethasone on CYP3A4 gene expression and PXR in human hepatocytes, at least 48 h were required to induce CYP3A4 gene expression, in contrast to the 12 h required for the induction of PXR mRNA expression (26). Inducers

require days or longer to be effective. Unlike induction, inhibition usually begins with the first dose of the inhibitor and is the highest at steady state (27, 28). Considering the half-life of dexamethasone, its effects on CES can be assessed by administering even low doses for 6 days.

Pharmacokinetic drug–drug interactions involve absorption, distribution, metabolism, and excretion. The potential sites of interaction include the gastrointestinal tract, tissue-binding sites, drug metabolizing enzymes, drug transporters, and renal excretion. In this study, oseltamivir and its active metabolite (oseltamivir carboxylate) reached their peak concentrations 0.5–4.0 h and 2.0–6.0 h after the administration of oseltamivir, respectively, irrespective of dexamethasone co-administration. In addition, the peak concentration and systemic exposure to oseltamivir in both treatments (oseltamivir alone or oseltamivir + dexamethasone) were similar. These results suggest that dexamethasone has a negligible effect on oseltamivir absorption. Interestingly, as shown in individual plots (Supplementary Figure 1), the second peak in the plasma concentration–time profile of oseltamivir following the major peak was observed in several subjects. Previous studies on the clinical PK of oseltamivir have also noted the double-peak phenomenon, which is considered to be due to enterohepatic recirculation (29, 30). It was not associated with the administration of dexamethasone. Furthermore, the double peak concentration of oseltamivir was not considered to have any significant impact on the PK of oseltamivir.

Several *in vitro* and *in vivo* studies have been conducted to determine the effects of dexamethasone on CES; however, conclusions from these studies

are inconsistent (23, 31-33). In the present study, we consider trends in the systemic exposure to oseltamivir carboxylate and the metabolic ratio after multiple administrations of dexamethasone, which was determined to be a CES inhibitor consistent with findings of previous studies. In a study of Quinney et al (2005), dexamethasone was shown to be a very weak inhibitor of CES at high millimolar concentrations through inhibition of CES1- and CES2-catalyzed hydrolysis of 4-methylumbelliferyl acetate (34). In addition, Takahashi et al. reported that dexamethasone weakly inhibits CES1-catalyzed imidaprilat formation from imidapril in human liver (23).

It is well known the activation of NRs, such as PXR, regulates the expression and activity of numerous drug metabolizing enzymes, including CYP3A4 and CES, which determine the PK and PD of various drugs. A study by Pascussi et al. demonstrated that dexamethasone is a ligand and an activator of human PXR, but only at supramicromolar concentrations (>10 μM) in human hepatocytes (26). In contrast, nanomolar concentrations of dexamethasone suppressed the expression of the CES genes in rat hepatocytes, and this suppression was reduced by glucocorticoid receptor (GR)-β, a dominant negative regulator of the GR (35). The PXR levels increased only at micromolar concentrations. In this study, low-dose dexamethasone may have inhibited the CES1 activity, resulting in decreased systemic exposure to the oseltamivir metabolite.

The activity of PXR may have reduced due to decreased glucocorticoid concentration according to the mechanism of maintaining homeostasis. Excess glucocorticoid concentration results in reversible

hypothalamic-pituitary adrenal axis suppression, leading to a decrease in glucocorticoid levels. The serum level of hydrocortisone in humans is 0.1–0.45 μM, and it maintains GR activation and thus the expression of PXR (26). However, the decreased production of hydrocortisone could suppress PXR and may result in the inhibition of CES1. The level of serum hydrocortisone after dexamethasone administration should be measured and compared with the basal status in further studies to interpret the results.

In contrast to systemic exposure, urinary levels and renal clearance of oseltamivir and oseltamivir carboxylate were increased, supporting the idea that dexamethasone affects the renal clearance of oseltamivir. Absorbed oseltamivir is primarily metabolized to oseltamivir carboxylate and then eliminated entirely by renal excretion (2). One possibility is that dexamethasone stimulates the clearance of oseltamivir carboxylate, leading to low plasma concentrations. A similar interaction has been proposed to occur when corticosteroids and salicylic acid are co-administered (36-38). However, an increased glomerular filtration rate and diminished tubular reabsorption of water after treatment with corticosteroids might partially explain their ability to increase the clearance of salicylate as well as the results observed for oseltamivir (39).

Although statistically significant, the 12% decrease in $AUC_{0\text{-}48h}$ observed for oseltamivir carboxylate is unlikely to be clinically relevant. Previous studies have shown that the approved adult treatment dose of 75 mg twice daily maintains concentrations exceeding the half-maximal inhibitory concentration (IC_{50}) values for all tested influenza strains by at least 50-fold (2). Furthermore, the recommended dosage to maintain the steady-state plasma

trough concentrations of oseltamivir carboxylate remains above the minimum inhibitory concentration for all the tested influenza strains (2). In a study by Eisenberg et al., the concentration of oseltamivir carboxylate in rat bronchoalveolar lining fluid was approximately 20-fold higher than that in plasma after 6 hours of oral administration of oseltamivir at 30 mg/kg. In addition, the penetration ratio was 1.51 and the apparent terminal half-life in rat bronchoalveolar lining fluid was more than 4 fold longer than that in plasma (40). Therefore, the observed decrease in AUC_{0-48h} for oseltamivir carboxylate should have little effect on the treatment outcomes, and a dose adjustment may not be necessary to produce the desired therapeutic effect in these cases.

The present study was conducted with low doses of dexamethasone. High-dose dexamethasone (3–6 mg/kg) treatment at the beginning of ARDS is an accepted therapeutic strategy (41). This study was not conducted in patients with influenza or ARDS, and we proceeded to low doses of dexamethasone in consideration of the safety of the healthy volunteers. In this regard, the dosage of oseltamivir also has not followed the standard treatment. Therefore, our results should be interpreted with caution. However, previous studies suggested that high-dose dexamethasone treatment in patients is likely to induce CES1 and increase the metabolism of oseltamivir, which may lead to clinically significant effects. Further studies evaluating the interaction between oseltamivir and dexamethasone in patients with influenza are required to verify these results.

The presence of wild type of c.662A>G SNP in all subjects enrolled in this study may be another limitation. The systemic exposure to oseltamivir

carboxylate was decreased in heterozygous allele carriers although it was not statistically significant. Moreover, in this study, the systemic exposure to oseltamivir carboxylate decreased after multiple administrations of dexamethasone. Based on these results, the reduction of body exposure to oseltamivir carboxylate by co-administration with dexamethasone is expected to be more prominent in heterozygous allele carriers.

In summary the co-administration of low-dose dexamethasone with oseltamivir marginally decreased systemic exposure to oseltamivir and oseltamivir carboxylate in healthy volunteers. This suggests that CES1 is inhibited by co-administration of low-dose dexamethasone and oseltamivir. However, the co-administration of low-dose dexamethasone and oseltamivir had no clinically relevant effects on the PK of oseltamivir. On the basis of these findings, we can conclude that low-dose dexamethasone can be co-administered with oseltamivir without dose adjustment.

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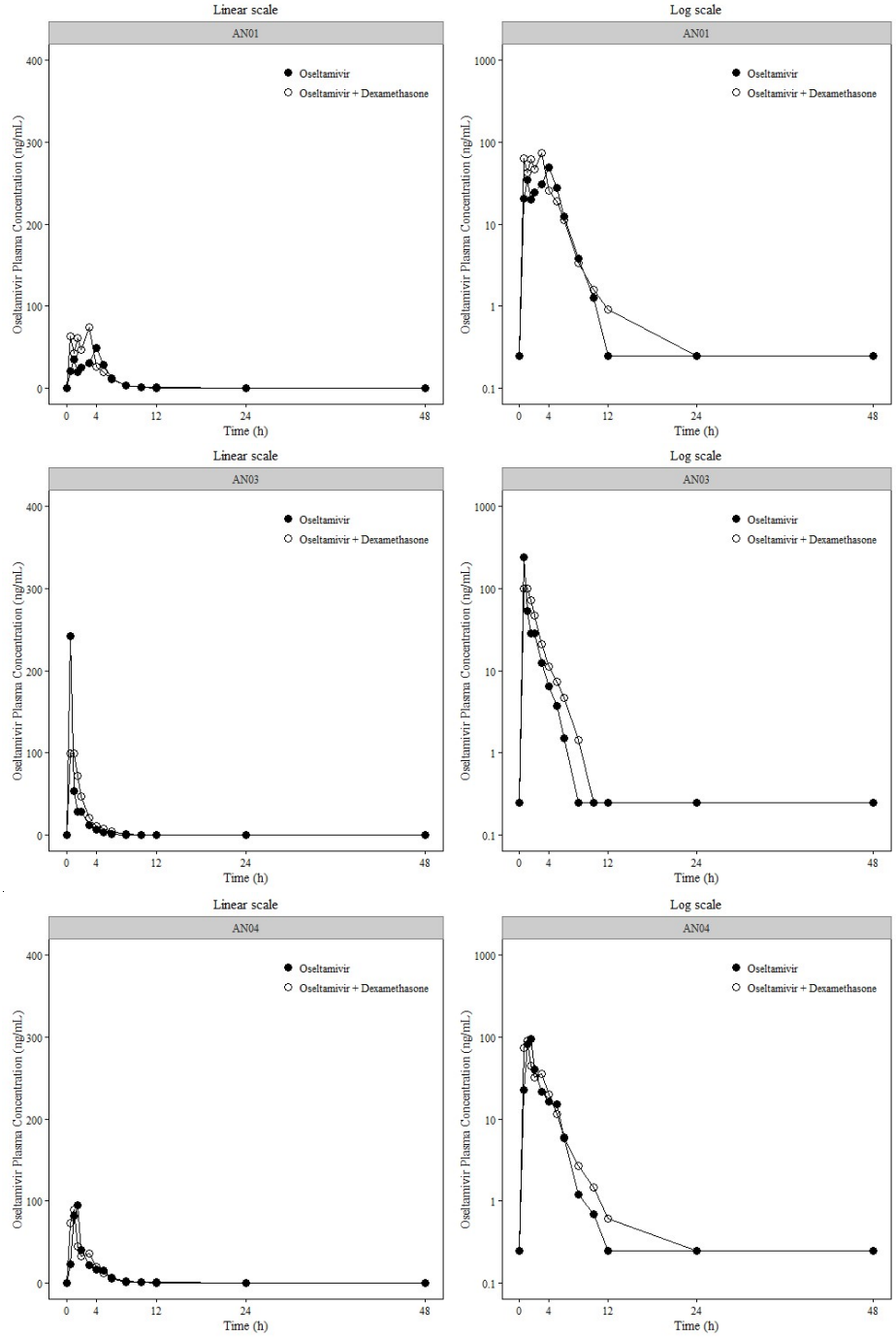
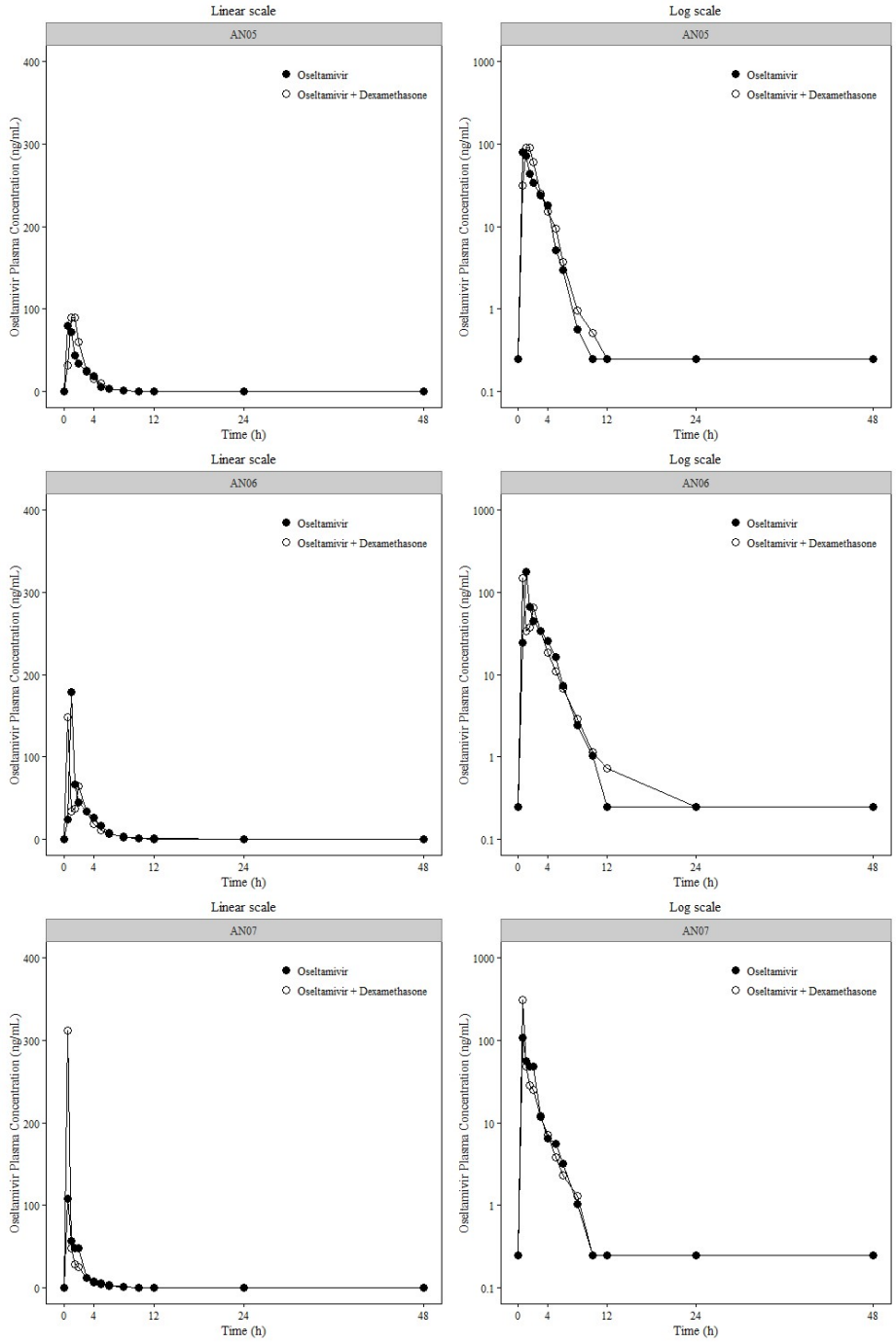
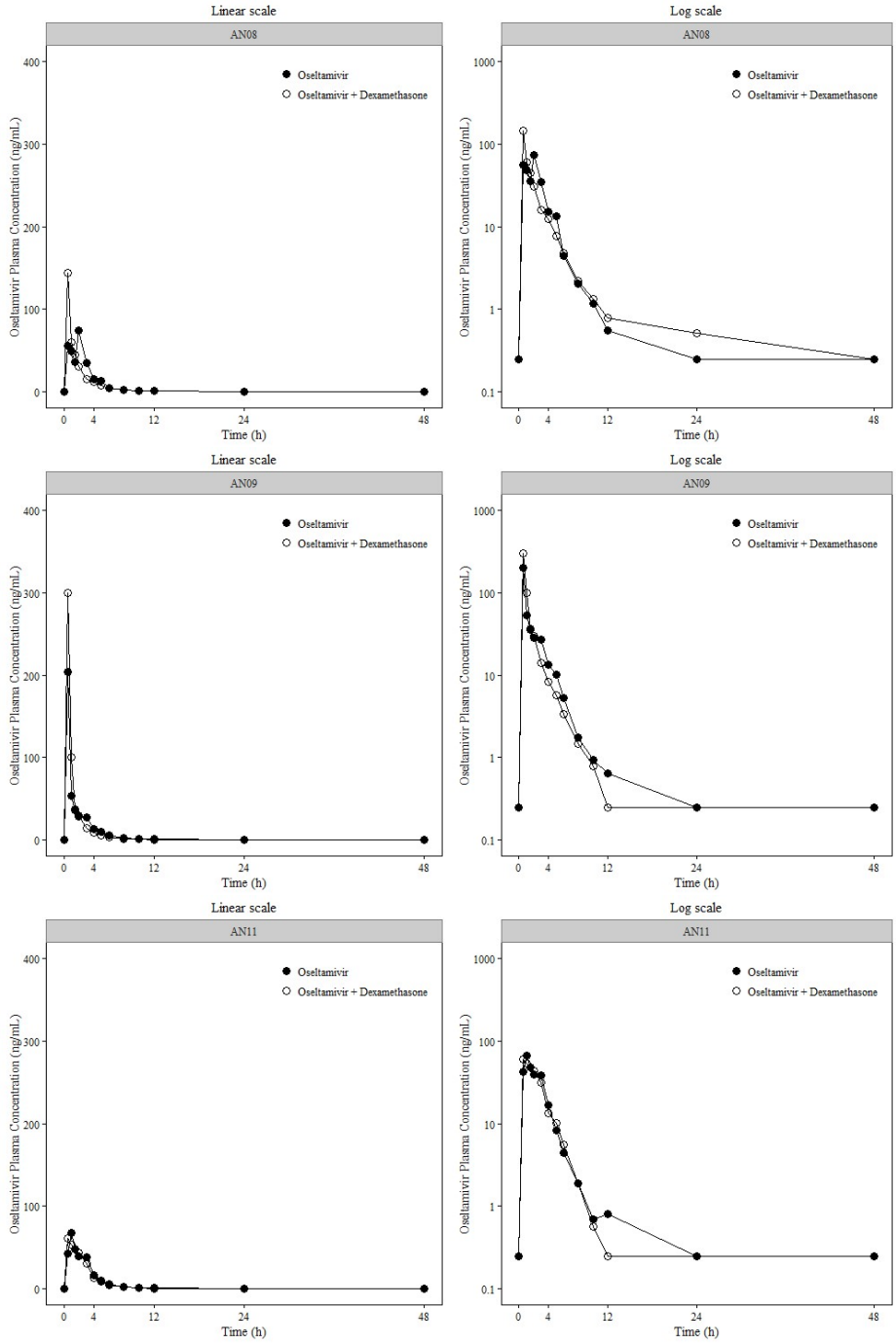
APPENDIX

Supplementary Figure 1. Individual plasma concentration-time profiles of oseltamivir




Linear scale
Log scale
AN05
AN06
AN07
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir Plasma Concentration (ng/mL)
Time (h)
0
4
12
24
48
0.1
1
10
100
1000
200
300
400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Log scale
AN08
AN09
AN11
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir Plasma Concentration (ng/mL)
Time (h)
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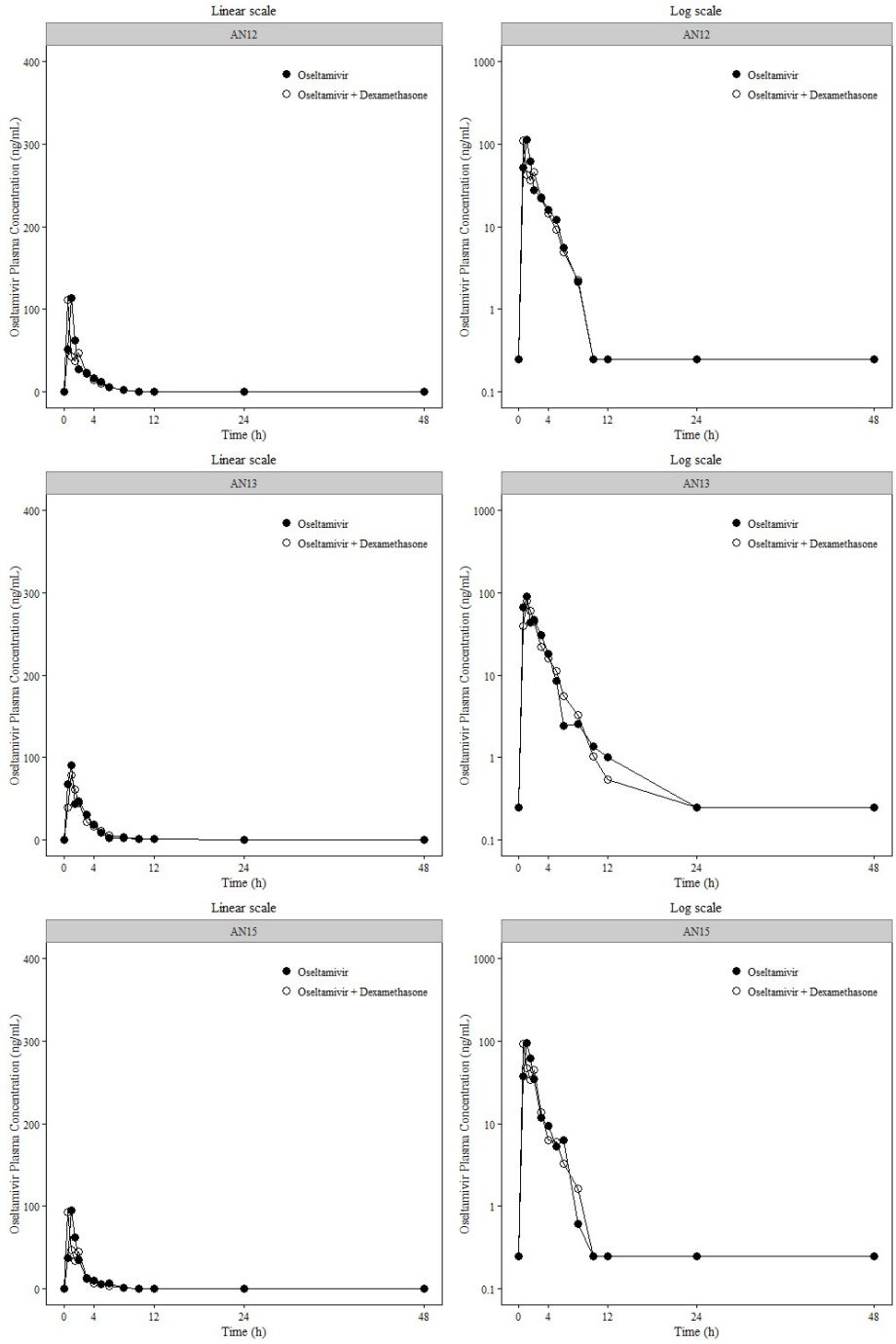
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Log scale
AN12
AN13
AN15
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir Plasma Concentration (ng/mL)
Time (h)
0
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12
24
48
0.1
1
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100
1000
200
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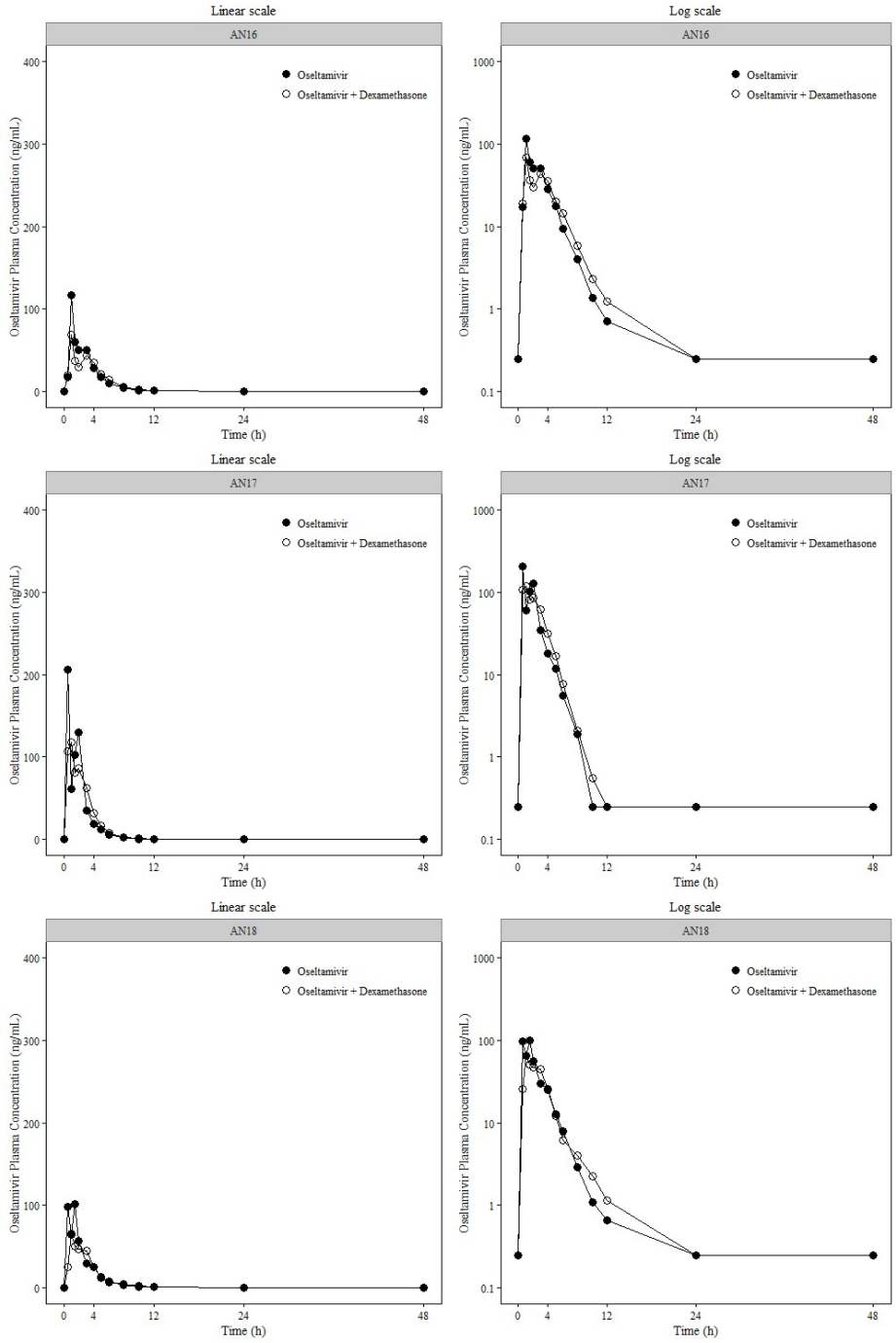
400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Log scale
AN16
AN17
AN18
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir Plasma Concentration (ng/mL)
Time (h)
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4
12
24
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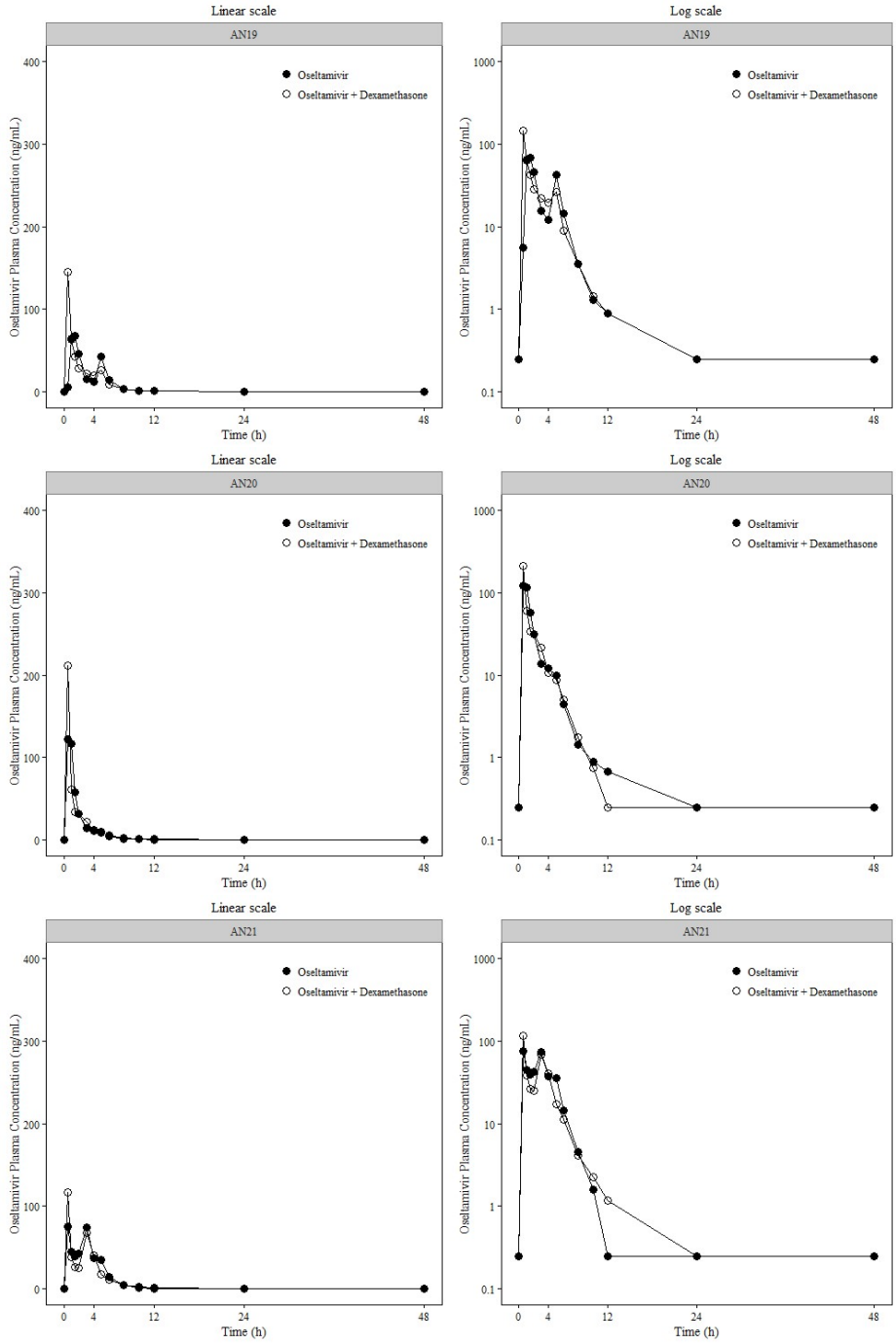
0.1
1
10
100
1000
200
300
400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Log scale
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AN20
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Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir Plasma Concentration (ng/mL)
Time (h)
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0.1
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100
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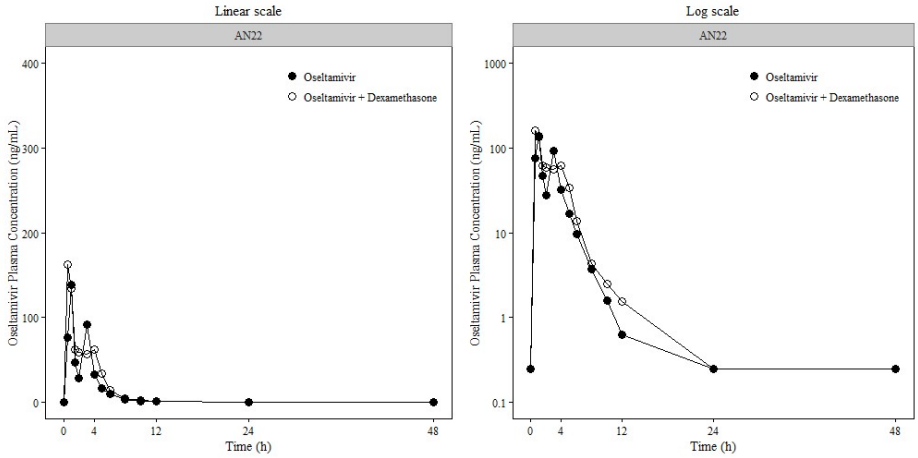
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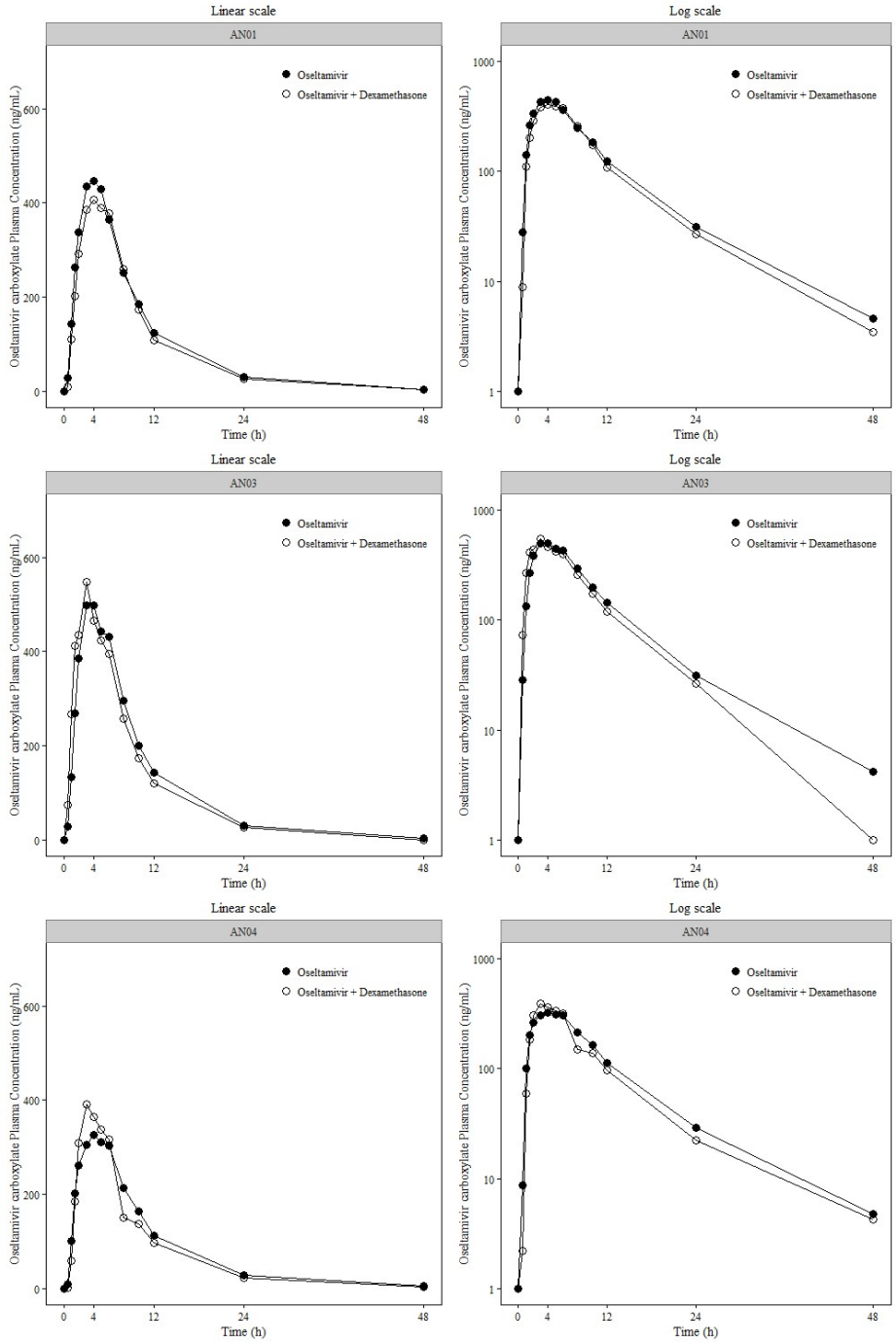
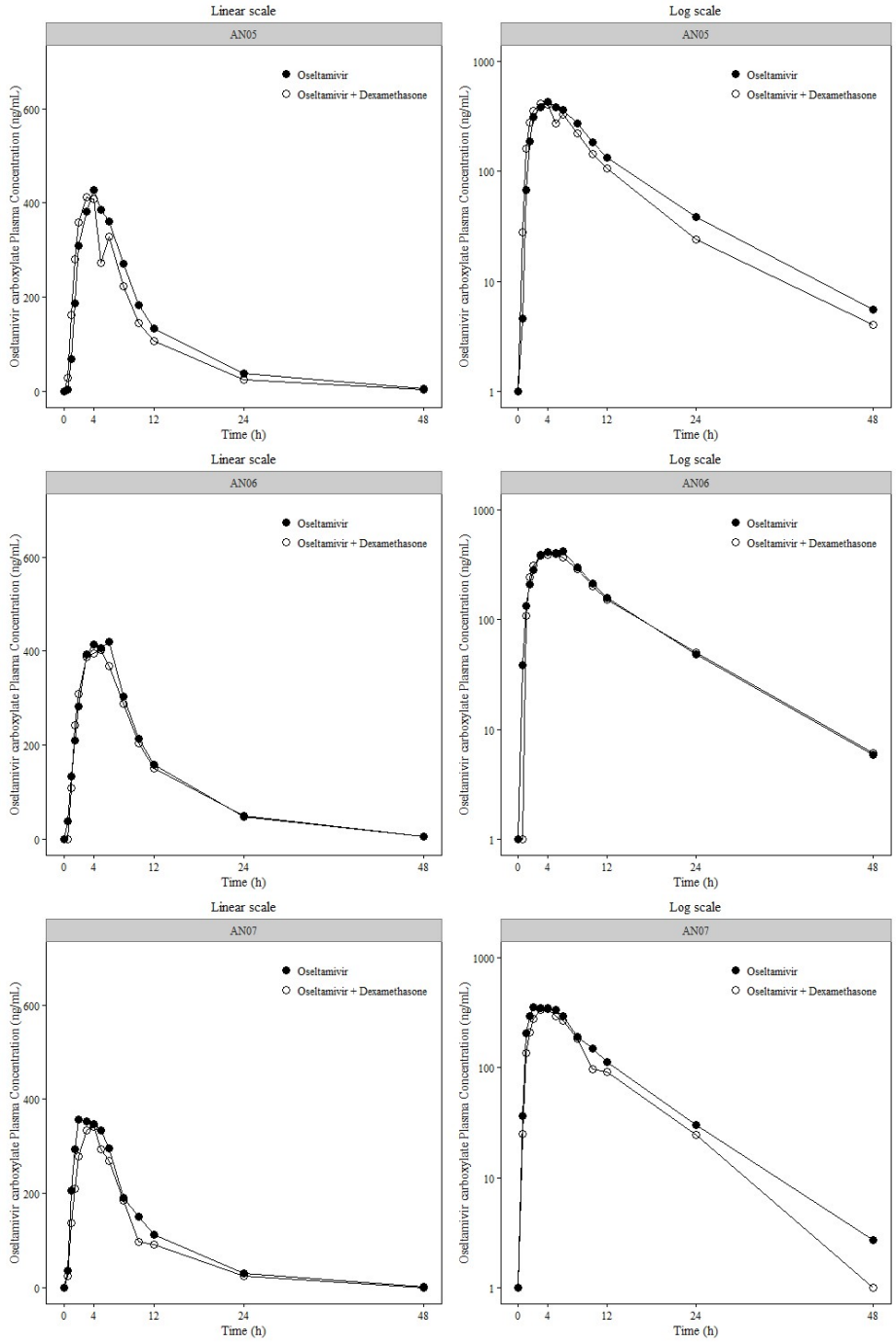
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir Plasma Concentration (ng/mL)
400
300
200
100
0
0
4
12
24
48
Time (h)
Log scale
AN22
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir Plasma Concentration (ng/mL)
1000
100
10
1
0.1
0
4
12
24
48
Time (h)

Supplementary Figure 2. Individual plasma concentration-time profiles of oseltamivir carboxylate




Linear scale
Log scale
AN05
AN06
AN07
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir carboxylate Plasma Concentration (ng/mL)
Time (h)
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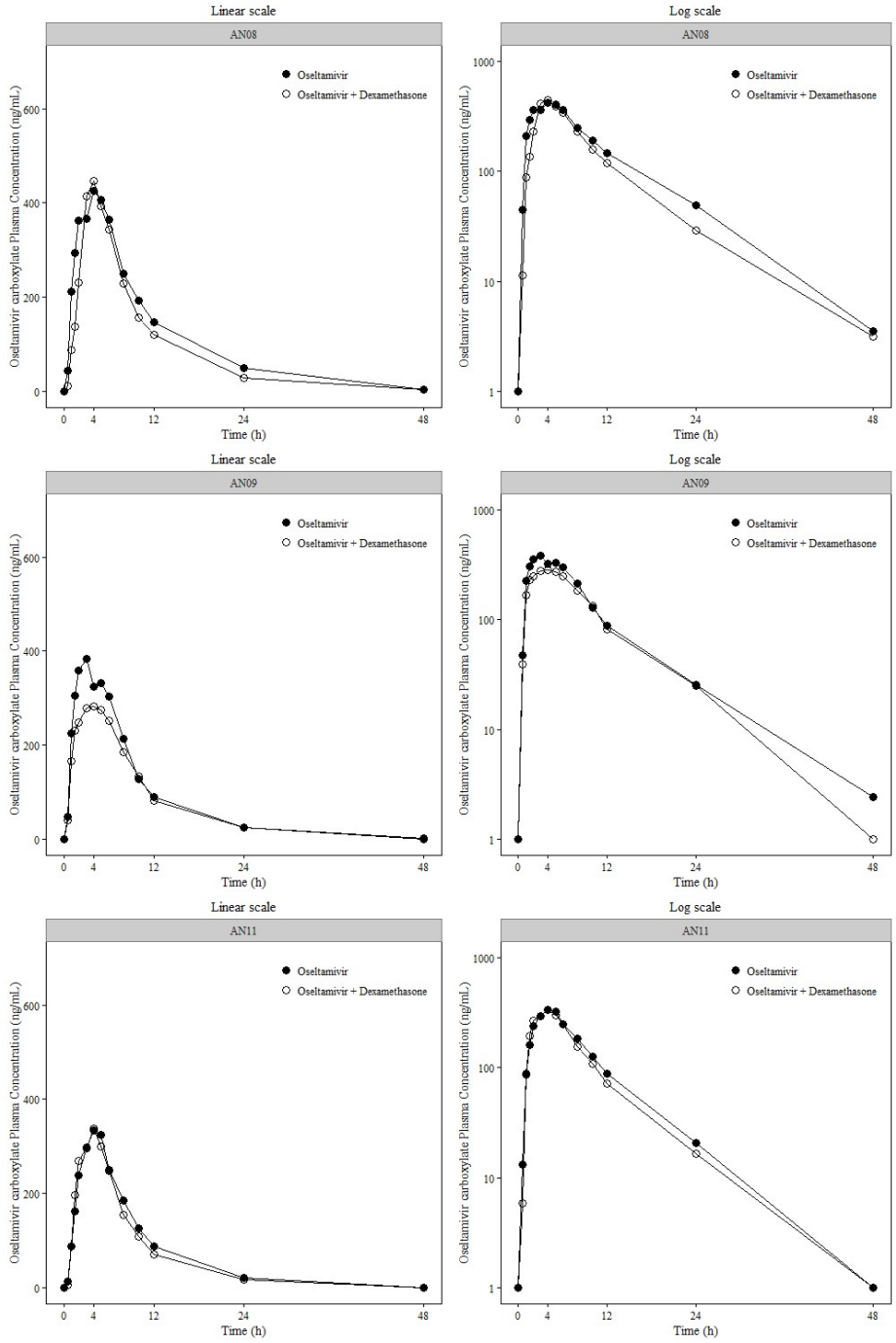
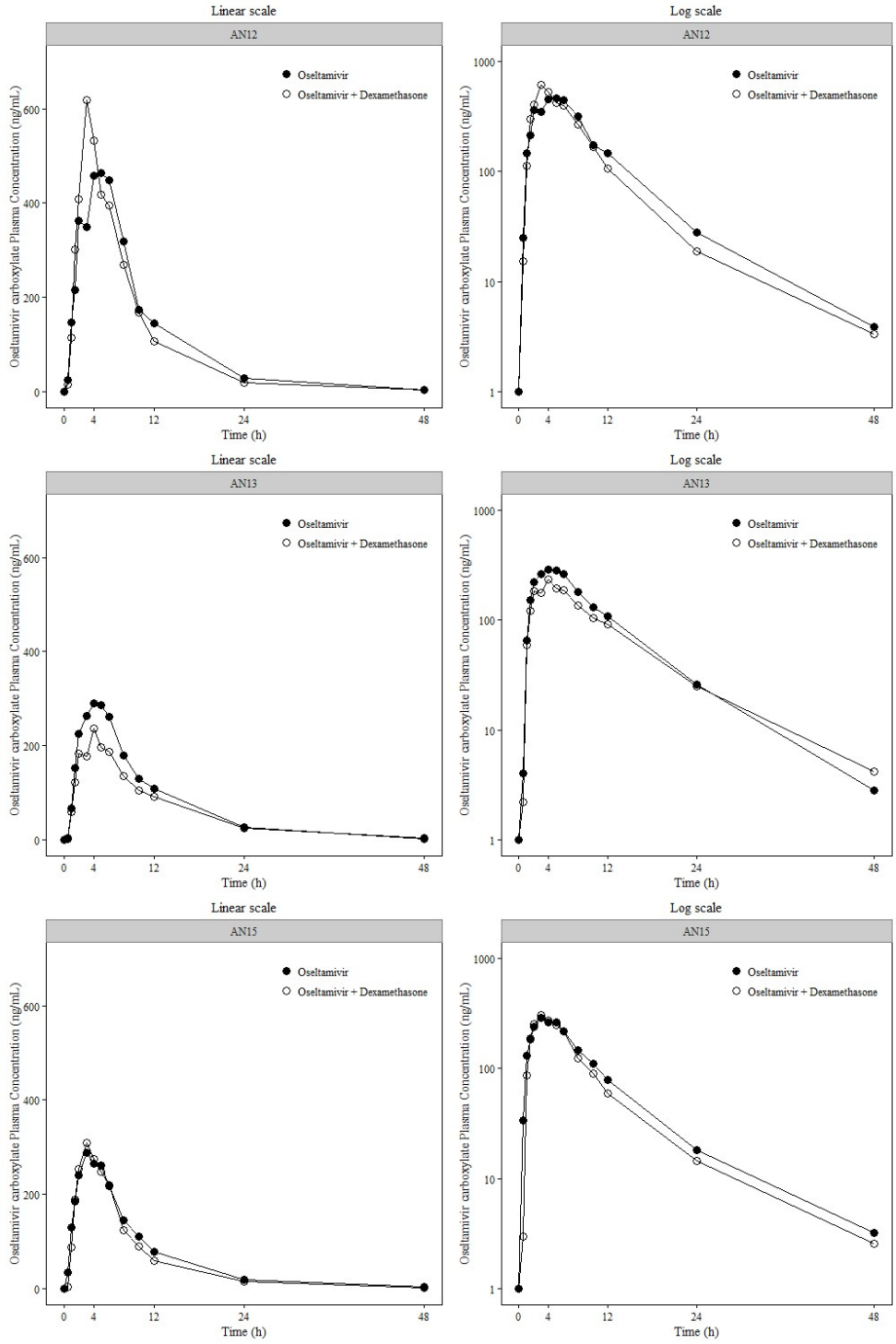
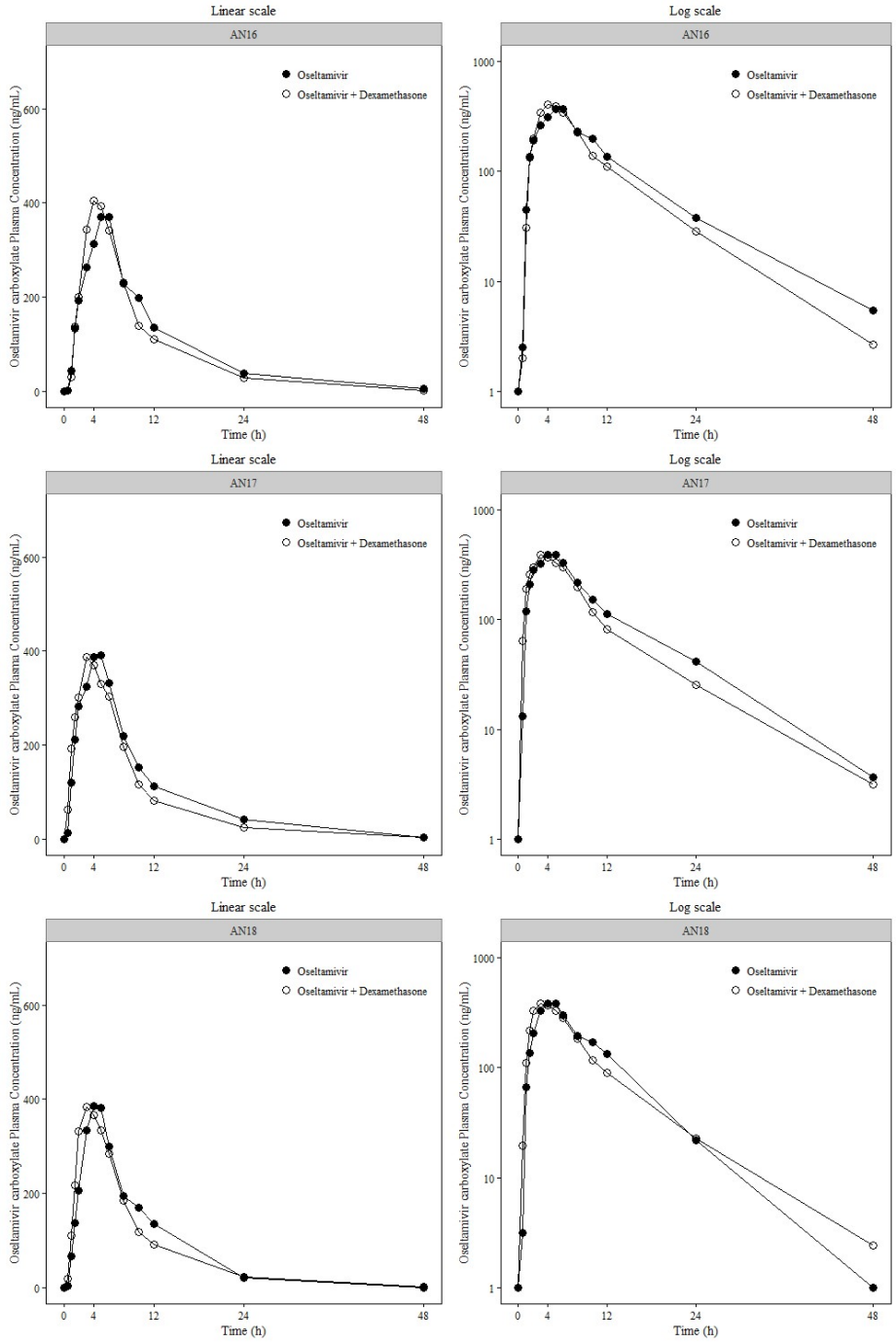
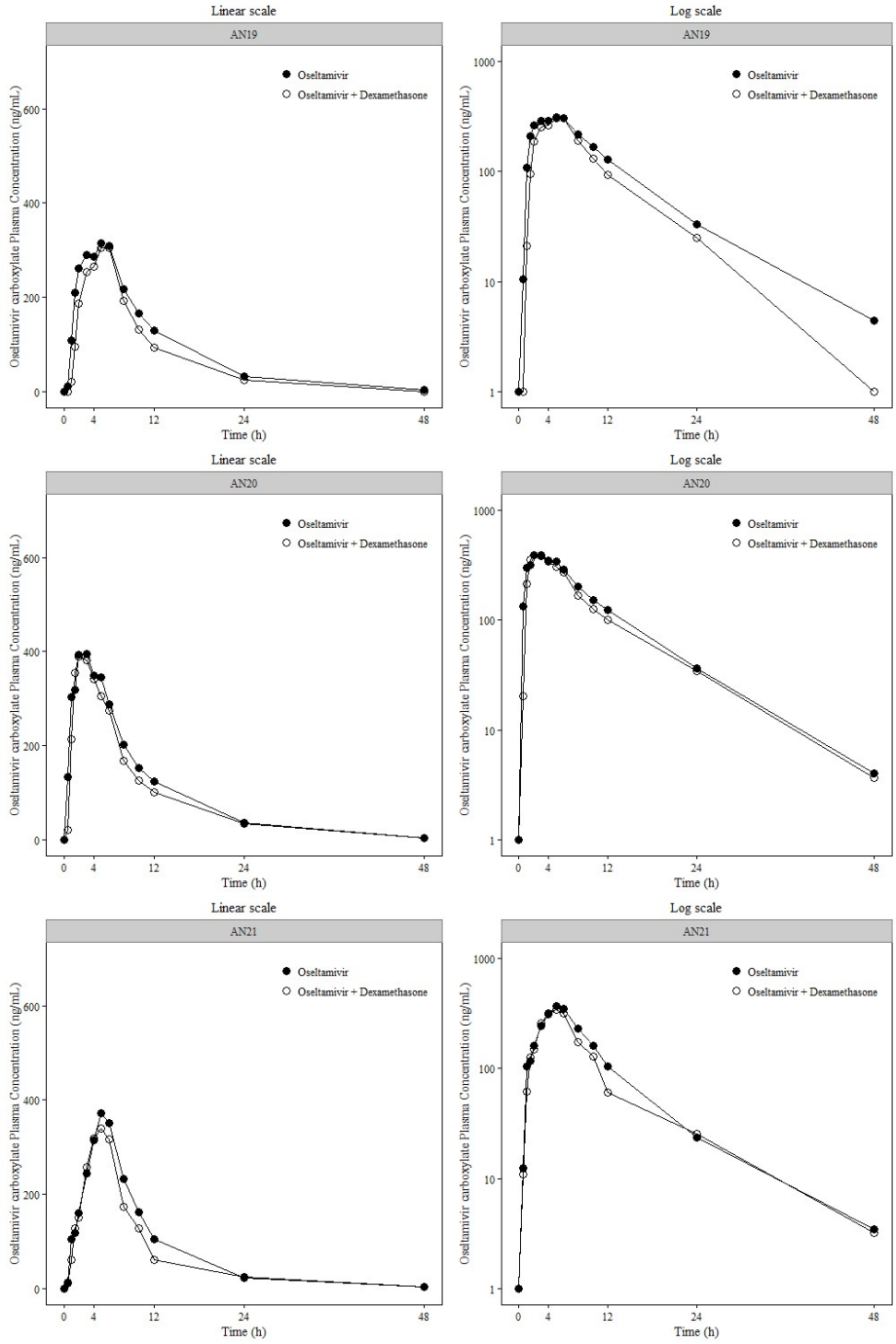
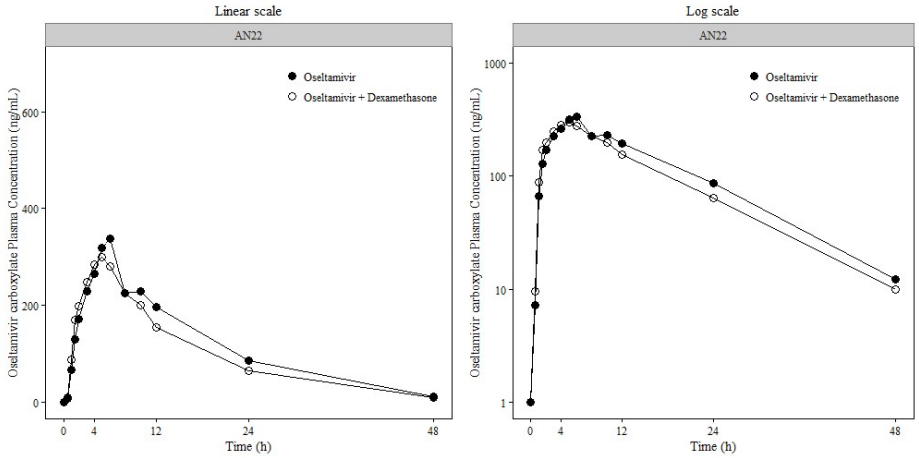
4
12
24
48
200
400
600
1000
100
10
1


Linear scale
Log scale
AN08
AN09
AN11
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir carboxylate Plasma Concentration (ng/mL)
Time (h)
0
4
12
24
48
1
10
100
1000
200
400
600


Linear scale
Log scale
AN12
AN13
AN15
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir carboxylate Plasma Concentration (ng/mL)
Time (h)
0
4
12
24
48
200
400
600
1000
100
10
1


Linear scale
Log scale
AN16
AN17
AN18
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir carboxylate Plasma Concentration (ng/mL)
Time (h)
0
4
12
24
48
1
10
100
1000
200
400
600


Linear scale
Log scale
AN19
AN20
AN21
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir carboxylate Plasma Concentration (ng/mL)
Time (h)
0
4
12
24
48
1
10
100
1000
200
400
600


Linear scale
AN22
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir carboxylate Plasma Concentration (ng/mL)
0
200
400
600
0
4
12
24
48
Time (h)
Log scale
AN22
Oseltamivir
Oseltamivir + Dexamethasone
Oseltamivir carboxylate Plasma Concentration (ng/mL)
1
10
100
1000
0
4
12
24
48
Time (h)

국문 초록

서론: 오셀타미비어는 인플루엔자 A 와 B 바이러스 감염의 예방 및 치료를 위하여 널리 쓰이고 있다. 덱사메타손은 인플루엔자의 중증 합병증인 급성 호흡곤란 증후군의 치료에 효과가 있다. 카르복실에스터라제 1 은 오셀타미비어를 주로 간에서 활성대사체인 오셀타미비어 카르복실레이트로 전환시키고, 덱사메타손은 카르복실에스터라제 1 의 발현을 조절하는 것으로 알려져 있다. 하지만 덱사메타손이 오셀타미비어의 약동학에 미치는 영향에 대해서는 아직 명확하지 않다. 본 연구의 목적은 사람에서 오셀타미비어와 병용투여한 덱사메타손에 의한 오셀타미비어의 약동학의 변화를 규명하기 위한 것이다.

방법: 19 명의 건강한 남성 자원자를 대상으로 공개형, 2 기, 반복투여의 방법으로 시험을 진행하였다. 모든 대상자들은 오셀타미비어 75 mg 을 제 1 일과 제 8 일에 각각 복용하였으며, 제 3 일부터 제 8 일까지 덱사메타손 1.5 mg 을 경구 복용하였다. 오셀타미비어와 오셀타미비어 카르복실레이트의 약동학 분석을 위하여 제 1 일과 제 8 일에 혈액 및 소변 샘플을 각각 수집하였고, 제 1 일에는 유전자형 검사를 실시하여 카르복실에스터라제 1 유전자형을 확인하였다. 혈장과 소

변에서의 오셀타미비어와 오셀타미비어 카르복실레이트의 농도는 액체 크로마토그래피 질량분석법을 이용하여 측정하였다.

결과: 저용량의 덱사메타손을 6 일 간 반복투여하였을 때, 덱사메타손 투여 후 오셀타미비어와 오셀타미비어 카르복실레이트의 혈중 노출량 (area under the concentration-time curve, AUC)은 각각 4% (P=0.21)와 12% (P<0.0001) 감소하였다. 대사율 (오셀타미비어 카르복실레이트 $AUC_{0\text{-}48h}$ / 오셀타미비어 $AUC_{0\text{-}48h}$)의 기하평균 비 (90 % 신뢰구간)는 0.92 (0.87−0.97; P = 0.02) 이었다. 덱사메타손 투여 후 소변으로 배출된 오셀타미비어의 양은 14% 증가하였다 (P=0.08).

결론: 본 연구의 결과는 저용량의 덱사메타손을 오셀타미비어와 병용투여 할 경우, 오셀타미비어 및 오셀타미비어 카르복실레이트의 체내노출이 감소할 가능성이 있음을 시사한다. 그 기전은 저용량의 덱사메타손이 카르복실에스터라제 1 을 억제하는 것으로 추정된다. 하지만 오셀타미비어의 체내노출 감소 정도가 임상적으로 유의한 치료효과의 감소를 나타낼 가능성은 적은 것으로 판단된다. 따라서 저용량의 덱사메타손은 오셀타미비어의 용량조절 없이 함께 투여할 수 있을 것이다.

주요어 : 오셀타미비어, 덱사메타손, 카르복실에스터라제, 약물상호작용

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